Birla Central Library
PILANI (Jaipur State)

Class No :- 547
Book No :- M821C
Accession No :- 32224

Acc. No . ...

ISSUE LABEL

Not later than the latest date stamped below.

INTERNATIONAL CHEMICAL SERIES
LOUIS P. HAMMETT, PH.D., *Consulting Editor*

* * *

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

The quality of the materials used in the manufacture of this book is governed by continued postwar shortages.

A SELECTION OF TITLES FROM THE
INTERNATIONAL CHEMICAL SERIES
LOUIS P. HAMMETT, PH.D., *Consulting Editor*

Amsden—
Physical Chemistry for Premedical Students

Arthur—
Lecture Demonstrations in General Chemistry

Arthur and Smith—
Semimicro Qualitative Analysis

Booth and Damerell—
Quantitative Analysis

Briscoe—
Structure and Properties of Matter

Coghill and Sturtevant—
An Introduction to the Preparation and Identification of Organic Compounds

Crist—
A Laboratory Course in General Chemistry

Daniels—
Mathematical Preparation for Physical Chemistry

Daniels, Mathews, and Williams—
Experimental Physical Chemistry

Desha—
Organic Chemistry

Dole—
Experimental and Theoretical Electrochemistry

Gibb—
Optical Methods of Chemical Analysis

Glasstone, Laidler, and Eyring—
The Theory of Rate Processes

Griffin—
Technical Methods of Analysis

Hamilton and Simpson—
Calculations of Quantitative Chemical Analysis

Hammett—
Physical Organic Chemistry
Solutions of Electrolytes

Henderson and Fernelius—
Inorganic Preparations

Huntress—
Problems in Organic Chemistry

Leighou—
Chemistry of Engineering Materials

Long and Anderson—
Chemical Calculations

Millard—
Physical Chemistry for Colleges

Moore—
History of Chemistry

Morton—
Laboratory Technique in Organic Chemistry
The Chemistry of Heterocyclic Compounds

Norris—
Experimental Organic Chemistry
The Principles of Organic Chemistry

Parr—
Analysis of Fuel, Gas, Water, and Lubricants

Reedy—
Elementary Qualitative Analysis
Theoretical Qualitative Analysis

Rieman, Neuss, and Naiman—
Quantitative Analysis

Robinson and Gilliland—
The Elements of Fractional Distillation

Schoch, Felsing, and Watt—
General Chemistry

Snell and Biffen—
Commercial Methods of Analysis

Steiner—
Introduction to Chemical Thermodynamics

Stillwell—
Crystal Chemistry

Stone, Dunn, and McCullough—
Experiments in General Chemistry

Thomas—
Colloid Chemistry

Timm—
General Chemistry
An Introduction to Chemistry

Watt—
Laboratory Experiments in General Chemistry and Qualitative Analysis

Williams and Homerberg—
Principles of Metallography

Woodman—
Food Analysis

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

by AVERY A. MORTON
Professor of Organic Chemistry
Massachusetts Institute of Technology

Second Impression

McGRAW-HILL BOOK COMPANY, INC.
NEW YORK AND LONDON
1946

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

COPYRIGHT, 1946, BY THE
McGRAW-HILL BOOK COMPANY, INC.

PRINTED IN THE UNITED STATES OF AMERICA

*All rights reserved. This book, or
parts thereof, may not be reproduced
in any form without permission of
the publishers.*

PREFACE

A generous third of the compounds listed in Beilstein have heterocyclic nuclei; over half of the types of compounds produced by nature have heterocyclic systems; the greater share of the drugs and medicinals and nearly all the alkaloids contain such structures; the large majority of the colors produced by nature and by man have these nuclei as essential components. Yet this wealth of chemical interest, and much more, is scarcely touched in the average textbook. Such compounds as are mentioned are usually treated as individual substances, not as members of a great class of compounds. And if classes of compounds are mentioned, the treatment is too sketchy to be worth while or to provide a working knowledge of the subject. Accordingly, the average student of organic chemistry comes to regard heterocyclic compounds as a very special field, to be entered if he desires to be a specialist of a kind, but certainly not to be eagerly studied as the fruition of his efforts to understand the principles of organic chemistry.

The aims of this text are to instill an appreciation of the chemistry of heterocyclic compounds and to create a realization that they are, after all, the logical continuation of the instruction in aliphatic and aromatic chemistry. The natural division of organic chemistry into aliphatic, aromatic, and heterocyclic chemistry is emphasized in the opening chapter, and the connections and interrelationships between these divisions are stressed repeatedly throughout the text. Appropriate comparisons and generalizations keep alive the knowledge acquired in the two better known fields and provide a bridge to understanding the new one.

The compilation of a text of this type presents several problems. For example, the representation of the various steps in the synthesis of many compounds might give the appearance of a book of formulas if one diagram were allotted to each step. Accordingly, the drawings have been limited, in general, to three or four key compounds, even though there may be as many as 10 or 20 steps from the simple known structures to the final product. With a little experience, the student will be able to recognize the sequence of reagents necessary to make the jump from one compound to the next. The details of the synthesis are, however, written in fine print. Large letters in place of formulas also conserve space and focus attention on the heterocyclic chemistry of a synthesis.

A second major problem is the reduction of an enormous field to textbook size. Generalizations have accordingly been employed extensively. A good example is in the discussion of the chemistry of the azoles. Chapter XIII is devoted entirely to the synthesis and properties of these compounds as a class. The author is well aware of the danger that such generalizations have. Every careful student of chemistry knows that organic compounds may have a highly specific action and that years of research may be required to confirm or deny the deductions from generalizations that appear obvious. Yet such generalizations provide the only method by which facts can be correlated and furnish suggestions for fruitful fields of research.

Numerous problems are included. The purpose is only partly to furnish a review of the discussion in the text. The large majority of these problems are new material, not mentioned in the text. They can be solved, however, if the principles discussed are understood; and their solution can be checked by the references given to the literature. The problems are, therefore, both a review and an extension. Their solution will fix the principles of this field firmly in the mind of the student, as few other methods of instruction are capable of doing.

The material is as comprehensive as the purpose of the book permits. No claim as a reference book is made, although the list of references is generous. But if the text is studied, a student will acquire a broad knowledge of the field, and if the problems are solved, he will gain a command of the principles of heterocyclic chemistry, which will enable him to appreciate the current problems and methods of solution.

The general viewpoint of the text is given in the opening paragraphs. In keeping with this view, the chemistry of monoheterocyclic rings is discussed first. The more complicated cases where more hetero atoms are present are then presented and the connection with the simpler type is discussed.

The author greatly appreciates the encouragement given by numerous friends during the preparation of the text. He also acknowledges the great inspiration given by his classes, which, over a period of many years, have uniformly shown a great interest in the subject and its correlation with the simpler divisions. He has been thus led to the belief that organic chemistry, as a whole, would be well served by a text which emphasizes this great field in its true role as one of the three outstanding divisions of organic chemistry and which gives a detailed picture of a wide variety of interesting and valuable compounds that are usually overlooked.

The author is especially indebted to Dr. Letsinger, to Miss Holden, and to Messrs, Ramsden, Redman, and Welcher, who have assisted in reading part of the proof.

AVERY A. MORTON.

CAMBRIDGE, MASS.,
March, 1946.

CONTENTS

PAGE

PREFACE v

CHAPTER

I THE FURAN COMPOUNDS 1

II CONDENSED FURAN SYSTEMS 20

III THIOPHENE AND CONDENSED THIOPHENE SYSTEMS 39

IV PYRROLES 56

V DI- AND POLY-PYRRYL COMPOUNDS. PORPHYRINS AND PHTHALOCYANINS 75

VI CONDENSED PYRROLE SYSTEM 100

VII PYRANS, PYRONES, AND RELATED COMPOUNDS . . 148

VIII THE PYRIDINE GROUP 185

IX PIPERIDINE AND RELATED COMPOUNDS 229

X THE QUINOLINE COMPOUNDS 262

XI ISOQUINOLINES 301

XII ACRIDINES AND OTHER CONDENSED COMPOUNDS . 326

XIII AZOLES, AZOLONES, AND RELATED SYSTEMS. PART I 362

XIV THE AZOLES. PART II. COMPOUNDS 418

XV THE AZINES AND RELATED COMPOUNDS 476

INDEX 521

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER I

THE FURAN COMPOUNDS

Organic chemistry can be divided into three great parts. The first, or aliphatic, part is concerned primarily with the behavior of comparatively simple systems such as the olefins, alcohols, aldehydes, acids, and amines. It might be called the chemistry of simple functional groups. The second, or aromatic, part covers the behavior of these functions when they are adjacent to an aromatic ring. The ring and the group have mutual effect upon each other, which makes aromatic compounds related to, but not identical with, the corresponding substances in the aliphatic class. The third, or heterocyclic, part comprises the behavior of these functions when they are part of the ring and when they are both part of and next to the ring. Heterocyclic chemistry is, therefore, a logical extension of aliphatic and aromatic chemistry; but the extra dimension makes the problem correspondingly complicated. It is not so complex, however, that the individual parts cannot usually be recognized and the chemistry appreciated in terms of the more familiar types. The study of the chemistry of this third great division provides, therefore, a thorough review of the principles of organic chemistry as a whole as well as an advance into a new and attractive field.

Heterocyclic chemistry can be regarded also as embracing a large percentage of bifunctional activity. When the two functions are propitiously situated, a heterocyclic ring results; when not so favorably placed, a polymer results. When one functional group is within a ring and the other is without, the activity of the latter is modified accordingly. The study of heterocyclic compounds is not, therefore, a study in a limited field set apart from the remainder of organic chemistry. It is rather an observation of organic chemistry in its broadest aspects.

In addition to the acquisition of a more thorough groundwork in organic chemistry, there is the added interest of acquiring an appreciation of the rich storehouse of organic compounds provided by nature; for a high proportion of heterocyclic compounds that have engaged the attention of chemists are the compounds that nature has provided. In many cases, this interest has, over a period of years, led to eminently practical results. The history of furfural furnishes an excellent example of this development. The discovery[1] of this compound in 1832 was merely the chance observation of an oily by-product in the preparation of formic acid from the action of sulfuric acid and manganese dioxide on sugar or starch. This oil was called *künstliches Ameisenöl,* or artificial oil of ants, from the association with formic acid. Eleven years later, an ounce of this oil was isolated[2] by treatment of 12 lb. of wheat flour or sawdust with sulfuric acid and water. Shortly after, the near-modern name of furfurol, indicative of its source from *Furfur Kleie* and *oleum,* was given.[3] By 1888,[4] its chemical ancestry had been traced to pentoses, such as arabinose and xylose, as illustrated below:

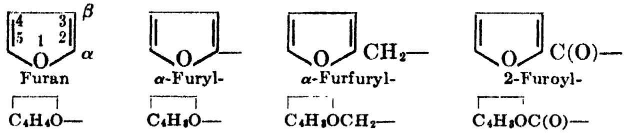
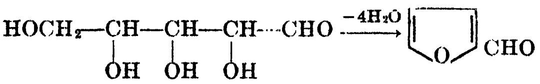


FIG. 1.—Numbering, naming, and simplified formulas of furan and some furan radicals.



Preparation of furfural was for years only a laboratory experiment or a method for analysis of pentosans.[5] In 1918, during experiments at the U.S. Bureau of Chemistry on the utilization of agricultural products, the customary analysis revealed as much as 26 per cent (dry basis) of furfural from an adhesive made from corncobs.[6] La Forge and coworkers[7] then found that corncobs themselves yielded 10 per cent furfural, when treated with superheated steam at 180°.

Simultaneously, a commercial laboratory perfected a process for its manufacture from oat hulls which has supplied the major demand since 1921. Production has increased to carload quantities, an impressive change,[8] indeed, from the 1 oz. obtained over a hundred years ago, and a change that is responsible for considerable interest in furan compounds.

[1] DÖBEREINER, *Ann.*, **3**, 141 (1832).

[2] STENHOUSE, *ibid.*, **35**, 301 (1840).

[3] FOWNES, *ibid.*, **54**, 66 (1845).

[4] STONE and TOLLENS, *ibid.*, **249**, 227 (1888).

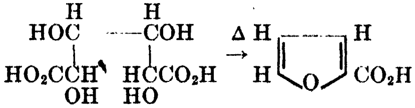
[5] BROWN, "Handbook of Sugar Analysis," p. 372, John Wiley & Sons, Inc., New York, 1912.

[6] MONROE, *Ind. Eng. Chem.*, **13**, 133 (1921).

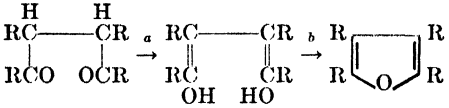
[7] LA FORGE, *ibid.*, **13**, 1024 (1921); **15**, 499 (1923); LA FORGE and MAINS, *ibid.*, **15**, 823, 1057 (1923); **16**, 356 (1924).

[8] PETERS, JR., *ibid.*, **28**, 755 (1936).

Synthesis of Furan Compounds.—The preparation of furfural from pentoses is paralleled by the formation of like products from other polyoses. The methyl pentoses, fucose and rhamnose, yield 5-methylfurfural. Hexoses yield 5-ω-hydroxymethyl-2-furfural[9] when heated with aqueous oxalic acid at 3 atm. pressure. Similarly, ordinary sugar, sucrose, treated with hydrochloric acid gives 5-ω-chloromethyl-2-furfural, which is easily reduced to 5-methylfurfural[10] by stannous chloride. The conversion of mucic to pyromucic acid by pyrolysis represents one more path from polyoses to furan compounds.



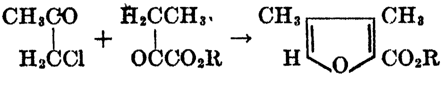
A second general source of furan compounds is by dehydration of appropriate 1,4-diketones or aldehydes according to the changes shown below.



R = H or other group.
[a] Enolization. [b] Dehydration with $ZnCl_2$, P_2O_5, or H_2SO_4.

Since 1,4-diketones can be prepared from ethyl sodioacetoacetates and iodine as well as by other ways, the process is widely adaptable.

In a third type of synthesis, ammonia, or better pyridine,[11] causes α-chloroketones to condense with ethyl acetoacetate or similar compound. If ammonia is used, pyrroles are simultaneously formed although with the relative position of chloroacetone with respect to the keto ester molecule inverted (see Chap. IV).



Alkylfurans.—Four methods for the preparation[12] of α-alkylfurans from furfural are shown in Fig. 2. The reactions are general and applicable to other systems besides furan. β-Furan compounds can usually be prepared by first blocking the alpha positions with carbethoxy, bromine,

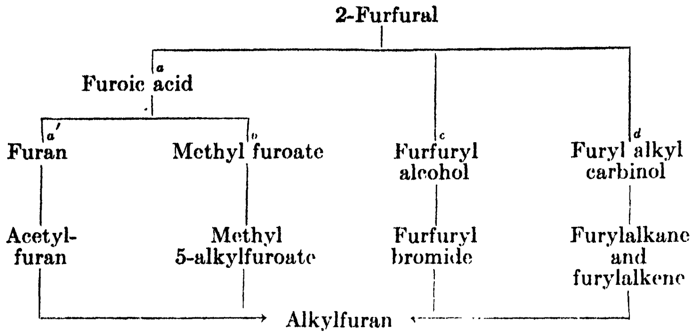
---

[9] Middendorp, *Rec. trav. chim.*, **38**, 1(1919); Teunissen, *ibid.*, **49**, 784 (1930).

[10] Rinkes, *Org. Syntheses*, **14**, 62 (1934); Coll. Vol. II, 393.

[11] Blomquist and Stevenson, *J. Am. Chem. Soc.*, **56**, 146 (1934); Scoll and Johnson, *ibid.*, **54**, 2549 (1932).

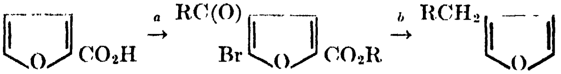
[12] Paul, *Bull. soc. chim.*, [5] **2**, 2220 (1935).



[a] Oxidation with $K_2Cr_2O_7$. [a'] Loss of CO_2 by pyrolysis, $CH_3COCl + AlCl_3$, Wolff-Kizhner reduction with hydrazine and alkali. [b] Esterification, alkylation by Friedel-Craft reaction, hydrolysis of ester, decarboxylation. [c] Reduction by H_2 over Ni, PBr_3, Mg, RX. [d] RMgX, dehydration over Al_2O_3 at 450°, reduction by Pt and H_2.

FIG. 2.—Methods for synthesis of 2-alkylfurans from furfural.

or other removable group, then introducing the beta substituent, and finally removing the alpha substituent, as shown below.



[a] Bromination, esterification, acylation. [b] Reduction of ketone with hydrazine and sodium ethoxide, hydrolysis of ester, decarboxylation, elimination of bromine by reduction.

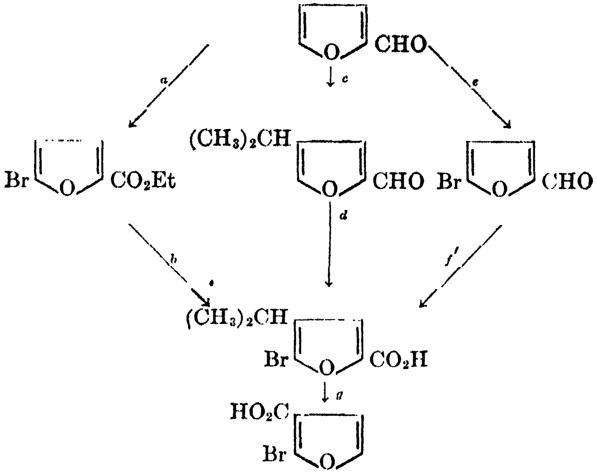
Orientation in the Furan Series.—Practically the only orientation[13] rule is that all substituting groups enter the alpha position if one is unoccupied. A strongly meta-directing group, such as nitro, carboxyl, or sulfonic acid, in one ortho position cannot prevent an entering group from taking the other alpha position. When both alpha positions are filled, the customary orienting influence is exerted at one of the two beta positions. Sulfonation of 5-bromo-2-furoic acid, for example, introduces the sulfonic acid group in the 4-, not the 3-, position. A group already in the beta position can also determine which of two open alpha positions will be substituted.

So universal is this rule of alpha substitution that any exception deserves special mention. Furfural, isopropyl chloride, and aluminum chloride give 4-isopropyl-2-furfural.[14] The structure is proved by an oxidation and reduction sequence that gives 5-bromo-4-isopropyl-2-furoic acid, identical with the product from two independent syntheses (Fig. 3) that begin by treatment of either 5-bromofurfural or ethyl 5-bromo-2-furoate with isopropyl chloride in a Friedel-Crafts synthesis. This substitution of the isopropyl group at C_4 is peculiar, for the several butyl chlorides and *n*-amyl chloride enter the alpha position[15] with simultaneous rearrangement to a tertiary alkyl form.

---

[13] GILMAN and BURTNER, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

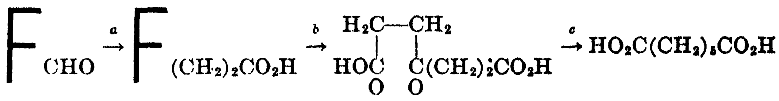
[14] GILMAN, CALLOWAY, and BURTNER, *ibid.*, **57**, 906 (1935).



[a] Oxidation, esterification, bromination. [b] $(CH_3)_2CHCl + AlCl_3$, hydrolysis. [c] $(CH_3)_2CHCl + AlCl_3$. [d] Oxidation, bromination. [e] Bromination. [f] $(CH_3)_2CHCl + AlCl_3$, oxidation. [g] Careful oxidation of the isopropyl group by bromination, hydrolysis of the polybromo compound, silver oxide oxidation, and potassium permanganate oxidation. The dicarboxylic acid is then treated with mercuric chloride.

FIG. 3.—Proof of irregular orientation of the isopropyl group in a Friedel-Crafts reaction with furfural.

Determination of Orientation of Furan Compounds.—Proof[16] that furfural is an α-substituted furan compound rests on a sequence of reactions (Fig. 4) for conversion to pimelic acid of known constitution. Furfural then serves as a reference point for judging the structure of a



Large F represents the furyl radical.

[a] Perkin synthesis with acetic anhydride and sodium acetate followed by reduction with sodium amalgam. [b] Ring opening and oxidation with bromine and silver oxide. [c] Reduction by hydriodic acid and phosphorus at 200 to 205°.

FIG. 4.—Conversion of furfural to an open chain compound.

large number of mono-substituted furans. Oxidation, for example, must produce an α-substituted acid. Furan and mercuric chloride, in the presence of sodium acetate, form a chloromercurifuran which, with iodine, yields iodofuran. This last compound, made into a Grignard reagent and carbonated, yields α-furoic acid. All compounds in this chain must, therefore, have been α-substituted. In like manner the position of other substituents in the furan nucleus can be established.

---

[15] Gilman and Burtner, *ibid.*, **57**, 909 (1935).

[16] Baeyer, *Ber.*, **10**, 355, 695, 1358 (1877).

In addition to such methods, the structure of a furan compound can be determined by synthesis from nonfuran compounds.

Reactions of the Furan Nucleus. *Substitution.*—Furan compounds undergo characteristic reactions of substitution, addition, replacement of oxygen, and ring opening. Substitution occurs much more easily than in benzene. Mercuric chloride, for example, attacks furan, forming monomercuric chloride derivatives which melt so sharply that they are valuable for identification (see Table 1). The reaction is usually accompanied by some disubstitution. Sodium-potassium alloy or potassium metal forms a small amount of furylpotassium[17] by reaction with furan. Thienylsodium and triphenylmethylsodium, which do not lose their metal to benzene, readily convert furan to furylsodium.

TABLE I.—MELTING POINTS OF SOME ALKYLFURYLMERCURIC CHLORIDES

Alkyl Substituent	Melting Point, °C
2-Methyl-5-	109
2-Ethyl-5-	99, 100
2-*n*-Propyl-5-	79–80, 81
3-Methyl-2	142
2-Isopropyl-5-	117–118
2-Isobutyl-5-	95–96
2-sec-Butyl-5	88
2-*t*-Butyl-5	136–137
2-Benzyl-5	121
3-Isopropyl-5-	90^-

Acylations are often accomplished with the aid of aluminum chloride, as in the benzene series, but may also be carried out with the help of such mild agents as zinc, stannic, titanium, and mercuric chlorides.[14] The furan nucleus is attacked so very easily that benzene can be used safely as a solvent in many Friedel-Crafts reactions.

Such vigorous processes as halogenation, nitration, and sulfonation are usually performed on substituted furans in which the presence of a benzoyl, carboxyl, or carbethoxy group reduces the tendency to form tars. The carbethoxy group has the double advantage of stabilizing the furan nucleus and of being easily removable when the reaction is concluded.

Substitution is not limited to replacement of the hydrogen atom. α-, but not β-, sodium carboxyl groups[18] give way to mercuric chloride under the influence of sodium acetate and mercuric chloride (if the free carboxyl group alone is present, the action is that of simple decarboxylation), and a carboxyl group can give way to an iodo (from iodine and

---

[17] GILMAN and BREUER, *J. Am. Chem. Soc.*, **56**, 1123 (1934).

[18] GILMAN, MALLORY, and WRIGHT, *ibid.*, **54**, 733 (1932); GILMAN and WRIGHT, *ibid.*, **55**, 3302 (1933).

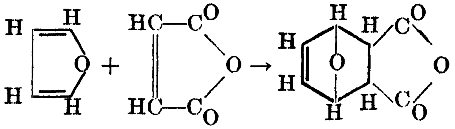
$$X{\cdot}C_4H_2O{\cdot}CO_2Na \xrightarrow{a} XC_4H_2OHgCl + CO_2 + NaCl$$

$$X{\cdot}C_4H_2O{\cdot}CO_2H \xrightarrow{a} XC_4H_3O + CO_2$$

[a] $HgCl_2 + NaOAc$.

potassium iodide) or a nitro group. An iodine atom is, in turn, replaceable by a nitro group, as in the change of 2,5-diiodofuran to 2-iodo-5-nitrofuran by treatment with nitric acid.

Addition Reactions.—Furan possesses a greater variety of addition reactions than does benzene. The butadiene character of the system is shown by addition of maleic anhydride[19] or dimethyl acetylenedicarboxylate. Halogens add[20] to the furan nucleus at low temperatures.



Ethyl furylacrylate, as an example, forms a dibromide at −15° which (*a*) decomposes spontaneously at a higher temperature to the α-bromo-derivative or (*b*) loses hydrogen bromide under the influence of alcoholic potash. So also does nitric-acetic acid form an addition compound.[21] Such reactions might be considered as circumstantial evidence of the general method of substitution by preliminary addition in compounds such as benzene as well as in furan. Furan, in fact, may represent a type intermediate between butadiene, to which halogens add, and benzene, in which they substitute.

Hydrogen readily adds to furan. At 100 to 150° and 100 to 150 atm. in the presence of Raney nickel, the reaction is strongly exothermic. A similar reduction is effected easily below 50° at 7 atm. over palladous oxide. The tetrahydrofuran[22] thus formed can be converted to 4-chlorobutanol, sometimes called tetramethylenechlorohydrin, by hydrochloric acid.

Ring Cleavage.—A mineral acid is the most common reagent for opening the ring. The reaction can be violent or moderate according to whether it is carried out with concentrated or dilute acid and whether it is performed on furan or a furan that contains a carboxyl or other stabilizing group. Furan reacts with explosive violence with concentrated hydrochloric acid but gives colors,[23] similar to those obtained with pyrrole, and a brown precipitate with dilute hydrochloric acid. Furfuryl alcohol also polymerizes with explosive violence when treated with concentrated acid but yields levulinic acid when subjected to the action of a 0.1 per cent solution of hydrochloric acid in methyl alcohol. Dialdehydes[24] or like compounds are probably the first hydrolysis products in all cases.

---

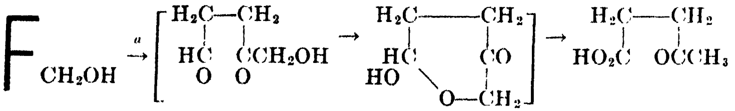
[19] DIELS and ALDER, *Ber.*, **62**, 554 (1929); *Ann.*, **490**, 243 (1931).

[20] MOUREU, DUFRAISSE, and JOHNSON, *Ann. chim.* [10], **7**, 8 (1927); GILMAN and WRIGHT, *J. Am. Chem. Soc.*, **52**, 3349 (1933).

[21] FREURE and JOHNSON, *ibid.*, **53**, 1142 (1931).

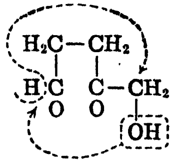
[22] STARR and HIXON, *Org. Syntheses*, **16**, 17 (1936); **17**, 84 (1937); Coll. Vol. II, 566, 571.

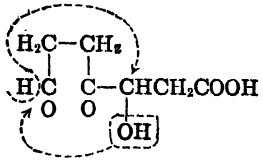
The steps in the formation of levulinic acid from furfuryl alcohol are usually assumed to include a hypothetical six-atom ring compound that



[a] Aqueous mineral acid.

functions as the medium for an interchange of groups—an intramolecular oxidation and reduction.[9] For convenience, this reaction can be represented as a simple position interchange of the H and OH groups on the opened ring as shown below. Similarly, furylacrylic acid, under the





influence of dilute alcoholic hydrochloric acid, first adds water to its double bond and then undergoes an interchange to the dimethyl ester of acetonediacetic acid.[25] This method has been recommended also for the synthesis of γ-ketonic acids, since the necessary secondary alcohol is prepared conveniently from furfural and a Grignard reagent.[26] When the alpha position is occupied by an aldehydo group, as in 5-ω-hydroxymethyl-2-furfural, the same interchange occurs but the aldehyde is separated in a hydrolytic process as formic acid. The reaction provides a method of distinguishing between hexoses and pentoses by the difference in the acids which they form. Formic acid will be found only if hexoses had originally been present.

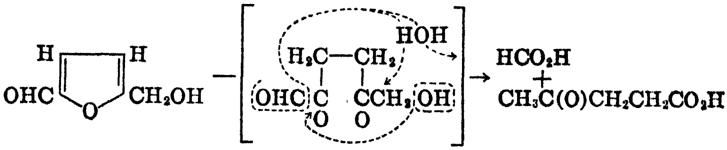
---

[23] LIMPRICHT, *Ann.*, **165**, 283 (1873).

[24] GILMAN and WRIGHT, *Chem. Rev.*, **11**, 328 (1932).

[25] MARKWALD, *Ber.*, **20**, 2811 (1887); VOLHARD, *Ann.*, **253**, 206 (1889).

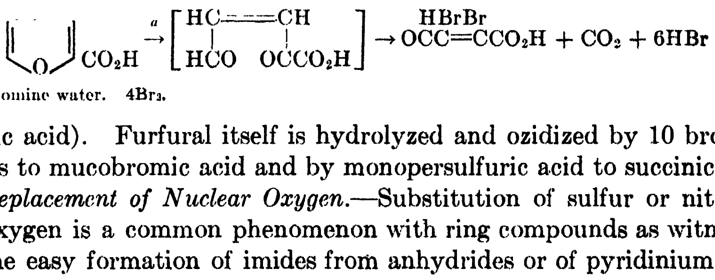
[26] CHICHIBABIN, *Chimie & industrie, Special No.* 563, March, 1932; PETERS, JR., and FISCHER, *J. Am. Chem. Soc.*, **52**, 2079 (1930).



So sensitive is furfuryl chloride to the least trace of acid that it decomposes when distilled in a flask that has been cleaned in an acid-cleaning bath and rinsed in the ordinary way.[27] Not until the flask has been washed repeatedly, stood overnight with distilled water, washed, and then steamed to remove every trace of acid can this compound be distilled.

As carboxyl, nitro, sulfonic, aldehydo, and ketonic groups enter the molecule, the action of hydrochloric acid becomes less vigorous. 2,4-Furandicarboxylic acid and 5-nitro-2-furfuryl methyl ether,[28] for example, are unaffected by this reagent; and furan compounds are actually formed from the action of fuming hydrochloric acid on phenacylacetone, $C_6H_5C(O)CH_2CH_2C(O)CH_3$, and diphenacyl,[29] C_6H_5-$C(O)CH_2CH_2C(O)C_6H_5$.

Oxidation opens the ring sometimes.[9] When furoic acid is treated with bromine water, carbon dioxide is evolved and mucobromic acid is formed. Chlorine similarly produces mucochloric (α,β-dichloroaldehydomaleic acid). Furfural itself is hydrolyzed and ozidized by 10 bromine atoms to mucobromic acid and by monopersulfuric acid to succinic acid.



[a] Bromine water. $4Br_2$.

Replacement of Nuclear Oxygen.—Substitution of sulfur or nitrogen for oxygen is a common phenomenon with ring compounds as witnessed by the easy formation of imides from anhydrides or of pyridinium from pyronium salts (see Chap. VII). The reaction is effected with some difficulty in the case of furan compounds. Nevertheless, passage of furan or α-methylfuran over aluminum oxide[30] at 450° with hydrogen sulfide or ammonia forms the corresponding thiophene or pyrrole. With aniline, under the same conditions, furan yields N-phenylpyrrole.

Superaromatic or Other Properties.—Superaromaticity[31] is a word used to emphasize the greater ease with which substitution occurs in furans and other classes of ring compounds as compared with that in the aromatic compound, benzene. Many examples, besides those mentioned under the substitution reactions, can be cited. Methyl benzoate cannot be alkylated or acylated easily, whereas methyl furoate is attacked by an alkyl halide and aluminum chloride or by acetic anhydride and ferric or stannic chloride.[32] Furyl phenyl ketone is acylated or nitrated exclusively in the furyl nucleus,[33] although the reagent has an equal chance at either part of the molecule. A furyl radical is eliminated more readily than a phenyl in the reaction of tetraaryl lead with hydrochloric acid. By similar tests, the thionyl nucleus is judged to be between furyl and phenyl.

---

[27] KIRNER, *J. Am. Chem. Soc.*, **50**, 1955 (1928).

[28] GILMAN and WRIGHT, *Chem. Rev.*, **11**, 346 (1932); GILMAN and BURTNER, *Iowa State Coll. J. Sci.*, **6**, 389 (1932).

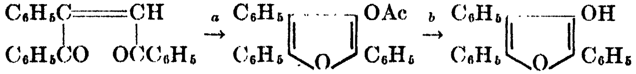
[29] PAAL, *Ber.*, **17**, 2759 (1884); KAPF and PAAL, *ibid.*, **21**, 1490, 3057 (1888).

[30] JURJEW, *ibid.*, **69**, 1944 (1936); JURJEW and RAKITIN, *ibid.*, **69**, 2492 (1936).

[31] GILMAN and TOWNE, *Rec. trav. chim.*, **51**, 1054 (1932); MEYER, "Die Thiophengruppe," p. 276, Brunswick, Friedrich Vieweg & Sohn, 1888.

$$R_4Pb + HCl \rightarrow R_3PbCl + RH$$

If the properties peculiar to an aromatic system are defined in terms of the relative ease of replacement, then it may indeed be said that furan is superaromatic. This limitation, however, must always be remembered. Many other properties characteristic of the aromatic types are absent in furan. Nothing resembling a phenol can be found in this heterocyclic system. α-Hydroxyfuran, if it occurs at all, immediately rearranges to a lactone. What might otherwise be looked on as a potential di-α-hydroxyfuran shows properties characteristic of a cyclic aliphatic anhydride only. Conversion of this anhydride to 2,5-dichlorofuran by reaction with phosphorus pentachloride, a reaction found repeatedly in many heterocyclic and enolizing systems, has never been realized. In the beta position, where the behavior is often more characteristic of aromatic systems, an acetyl derivative of 3-hydroxy-2,4,5-triphenylfuran (Fig. 5) has been isolated, but the free hydroxyl derivative[34] behaves as an enol in the ordinary enol-keto tautomeric system.



[a] Acetic anhydride and sulfuric acid close the ring and introduce the acetyloxy group. [b] The ester is cleaved under anhydrous conditions by means of the Grignard reagent followed by dry hydrochloric acid. Note the method of "hydrolysis" without the use of water.

FIG. 5.—Reaction sequence for the preparation of hydroxytriphenylfuran.

Neither are α-amino derivatives[35] easily prepared, very stable, or successfully diazotized, so that the vast field of diazo compounds, so characteristic of the benzene system, is absent. True, it is possible to diazotize β-amino compounds, *viz.*, ethyl 4-amino-5-acetamino-2-furoate,

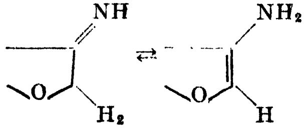
[32] GILMAN and CALLOWAY, *J. Am. Chem. Soc.*, **55**, 4197 (1933).

[33] GILMAN and YOUNG, *ibid.*, **56**, 464 (1934).

[34] KOHLER, WESTHEIMER, and TISHLER, *ibid.*, **58**, 264 (1936).

[35] GILMAN and WRIGHT, *Rec. trav. chim.*, **53**, 13 (1934); RINKES, *ibid.*, **51**, 349 (1932); STEVENSON and JOHNSON, *J. Am. Chem. Soc.*, **59**, 2525 (1937).

3-amino-2-methylfuran, and 3-amino-2,5-dimethylfuran and couple the products with β-naphthol to form a dye, but the Gattermann reaction with copper and hydrobromic acid produces no bromo derivative. Copper and hydrocyanic acid cause substitution by a hydroxyl group that changes directly to the keto form. These amino groups are sensitive to the action of hot aqueous acids and alkalies. Hot dilute sulfuric acid separates the nitrogen quantitatively as ammonia. The behavior of the last two amines with methylmagnesium iodide points to the existence of a ketimine-enamine system.



Another characteristic of aromatic systems, notably the directing influence of groups, is conspicuously ineffective when opposed by the tendency toward substitution in the alpha position.

Far from being fenced in by aromatic properties, furan can behave as if it were entirely devoid of them. Indeed, some workers prefer to consider the system as an *internal ether* of a diene, which exhibits sensitivity to acids and resistance to alkalies in common with all ethers and shows additive reactions and 1,4-addition peculiar to dienes.

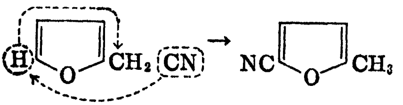
This viewpoint, particularly that of an ethereal oxygen atom, is, in general, of the type emphasized in this text. The oxygen atom is regarded as an ether system within the ring, modified somewhat by resonance. Its influence should therefore be related to that of an ether outside the ring, as in anisole or the dimethyl ether of resorcinol. Movement of the oxygen atom from a point without to one within the nucleus should intensify the usual activating influences[36] that such a group has. To a high degree, this result is found. Anisole is substituted readily by all common reagents such as the halogens or mercuric acetate; furan is substituted even more readily. The preferred position in anisole is ortho and para to the methoxy group; the preferred position in furan is ortho to the ethereal oxygen atom, *i.e.*, the alpha position. Anisole is readily attacked by an organoalkali reagent; furan is even more readily attacked and undergoes dimetalation. If a hydroxy group is somehow introduced by an indirect method in a furan system, tautomerism occurs and the product exists entirely in the keto form, a lactone if in the alpha position. If a hydroxyl group is similarly placed meta in anisole or the dimethyl ether of resorcinol, tautomerism occurs readily, and the product can act as a ketone with an active methylene group that can form an oxime, undergo alkylation with methyl iodide and alkali, or show other typical reactions. The keto form of the hydroxy furan is, therefore, merely the extreme end of a trend already well marked.

---

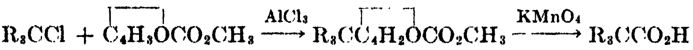
[36] MORTON and PATTERSON, *ibid.*, **65**, 1346 (1943).

Presentation of furan as a superaromatic compound or as a cyclic butadiene ether serves a useful purpose, if such correlations suggest possibilities of new reactions. The more such comparisons, the more fruitful organic chemistry becomes. Failure of furan to be exclusively aromatic should not be permitted to interfere with useful predictions that can be made from such an approach. On the other hand, the limitations of any group with which furan is compared should not be allowed to circumscribe the unique possibilities of this heterocyclic compound. The fact is that furan does not have to be considered either as superaromatic or as an unsaturated cyclic ether. Furan occupies a niche of its own and, as will be emphasized below, has properties peculiar to furan.

Rearrangements.—Rearrangement accompanied by ring opening has already been described in connection with the formation of δ-substituted levulinic acids from furfuryl alcohols. A similar change without ring opening occurs when furfuryl chloride is treated with sodium cyanide.[37] The product is a cyanomethylfuran instead of the expected furfuryl nitrile. A corresponding effect is not known in the benzene series.



Preparation of Nonfuran Products from Furan Compounds.—Heterocyclic compounds are frequently very useful as sources of nonheterocyclic materials. The preparation of levulinic acid and like compounds and the formation of mucobromic acid have already been cited. Tertiary carboxylic acids[38a] can readily be obtained by the action of a tertiary alkyl halide on methyl furoate in the presence of aluminum chloride followed by a permanganate oxidation that destroys the furan ring.



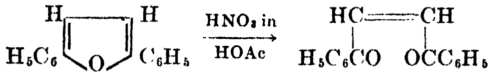
$$R_3CCl + C_4H_3OCO_2CH_3 \xrightarrow{AlCl_3} R_3CC_4H_2OCO_2CH_3 \xrightarrow{KMnO_4} R_3CCO_2H$$

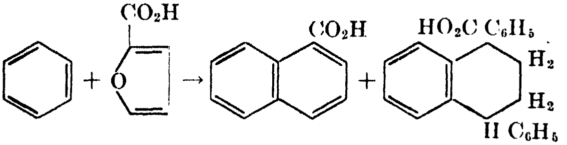
The method is preferable to the Grignard reaction which frequently gives low yields. Nitric–acetic acid oxidation of 2,5-diphenylfuran gives a cis unsaturated 1,4-diketone.[38b] The method depends on oxidation before enolization when the ring is opened. Benzene, 2-furoic acid, and aluminum chloride form a little α-naphthoic acid (10 per cent yield), considerable (60 per cent yield) 1,4-diphenyl-1,2,3,4-tetrahydro-1-naphthoic acid, and other products.[38c] Chlorobenzene, toluene, and anisole form a 6-substituted-1-naphthoic acid. Dehydrogenation and decarboxylation of the tetrahydro compound give 1,4-diphenylnaphthalene.

---

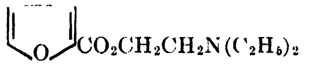
[37] RUNDE, SCOTT, and JOHNSON, *ibid.*, **52**, 1284 (1930); REICHSTEIN, *Ber.*, **63**, 749 (1930).

[38] (*a*) REICHSTEIN, ROSENBERG, and EBERHARDT, *Helv. Chim. Acta*, **18**, 721 (1938); (*b*) LUTZ and WILDER, *J. Am. Chem. Soc.*, **56**, 978 (1934); (*c*) PRICE and coworkers, *ibid.*, **63**, 1857 (1941).





Physiological Activity of the Furan Compounds.—Substitution of a furan for a benzene nucleus in compounds that usually are physiologically active decreases the activity. Diethylaminoethyl 2-furoate[39] is the furan analogue of novocaine (procaine), save for the *p*-amino group in the latter. An amino group is not necessary for anesthetic action and is, moreover, difficult to introduce in the furan nucleus. If novocaine is rated on a basis of 10, diethylaminoethyl benzoate is 4, and diethylaminoethyl furoate is less than 1. The furan nucleus is, in fact, the least active of any of the mono hetero five-atom systems since the corresponding thiophene and pyrrole compounds have ratings of 1 and 2, respectively.



Comparison of the hypnotic action of methyl 2-furyl ketones and others[39] with acetophenone shows that substitution of phenyl by pyrryl, thienyl, and furyl causes a progressively marked decrease in activity.

Ethyl 2-furoate itself has a noticeable anesthetic action. Failure of the dimethylaminoethyl furoate is, therefore, impressive, since the corresponding compounds in the benzoate series show increased activity when the dimethylamino group is inserted in the molecule.

Compounds in the Furan Series.—The history of the discovery of *furfural* was given at the beginning of this chapter. Its formation is quantitative when pentosans are distilled rapidly with 12 per cent hydrochloric acid saturated with salt.[40] It is found also among the products from the dry distillation of wood[41] and has been detected even in the glacial acetic acid[42] from that source.

---

[39] Gilman and Pickens, *J. Am. Chem. Soc.*, **47**, 245 (1925); Gilman, Rowe, and Dickey, *Rec. trav. chim.*, **52**, 395 (1933).

[40] Hughes and Acree, *Bur. Standards J. Research*, **21**, 327 (1938).

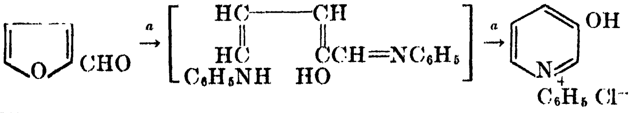
Furfural shows all the typical reactions of the aldehyde group. It adds bisulfite, oxidizes (potassium dichromate) to furoic acid, reduces readily to furfuryl alcohol, undergoes the Cannizzaro reaction with 33 per cent sodium hydroxide, forms furoin analogous to benzoin with potassium cyanide, reacts with ammonia to form furfuramide,

$$\overline{C_4H_3O}CH(N{=}CH\cdot\overline{C_4H_3O})_2,$$

and forms a Schiff's base with aniline. Direct removal of the aldehyde group with formation of furan occurs over soda lime[43] at 350 to 360° or over finely divided nickel[44] at 200°.

The chief uses[8] of furfural are for the preparation of resins by combination with phenol, for the purification of wood rosin by extraction of colored substances from a petroleum solution, and for the removal of undesirable components from petroleum oils. The comparative insolubility of furfural and petroleum in each other at low temperatures is the basis for the last two uses.

Furfural is determined quantitatively by precipitation of a condensation product with phloroglucinol, thiobarbituric acid, or 2,4-dinitrophenylhydrazine. It can also be measured by addition of bromine (bromide-bromate) to the double bond. The same methods are applicable to 5-methylfurfural.[45] A qualitative test,[46] applicable to all α-furaldehydes, is made with aniline. The red color produced is caused by ring opening with the ultimate formation of N-phenyl-β-hydroxypyridinium chloride according to the following sequence:



[a] $2C_6H_5NH_2 + HX$.

About 50 grams of 5-*ω-hydroxymethylfurfural* can be obtained from a kilogram of sugar as a result of the action of oxalic acid at 134°. Its formation was missed for a long time until the product was subjected to distillation (b.p. 114 to 117°/1 mm.) in a good vacuum. Hydrolysis leads to levulinic and formic acids. Since these acids, along with humus, are the final products of the action of warm mineral acids on mono- and di-saccharides, this aldehyde may represent an intermediate step. The red color test given by hexoses in the presence of resorcinol and concentrated hydrochloric acid can be attributed to the same intermediate.

---

[41] Meyer, *Ber.*, **11**, 1870 (1878).

[42] Hill, *Am. Chem. J.*, **3**, 33 (1881).

[43] Hurd, Goldsby, and Osborne, *J. Am. Chem. Soc.*, **54**, 2532 (1932).

[44] Pringsheim and Noth, *Ber.*, **53**, 114 (1920).

[45] Iddles and French, *Ind. Eng. Chem., Anal. Ed.*, **8**, 283 (1936).

[46] Stenhouse, *Ann.*, **156**, 197 (1870); Youngburg and Pucher, *J. Biol. Chem.*, **61**, 741 (1924).

Furfuryl alcohol is obtained by reduction of the aldehyde. In contact with strong mineral acids and even with formic acid, it polymerizes with explosive violence. The resin can be developed[8] on the wood by first painting the surface with the alcohol and then applying 15 per cent sulfuric acid.

TABLE II.—PHYSICAL PROPERTIES OF SOME FURAN COMPOUNDS

	M.P., °C.	B.P. °C.	Mm.
Furan	.....	31.4	756
2-Methylfuran	.....	62.5	737
3-Methylfuran	.....	65.5	
Furfural	−36.5	161.7	
5-Methyl-2-furfural	.....	187	
5-Hydroxymethyl-2-furfural	31.5	114	1
Furfuryl alcohol	.....	171	750
2-Furoic acid	133	130	50
3-Furoic acid	120.5	105	12
5-Bromo-2-furoic acid	186		
Nitrofuran	28.8		

Furoic acid, known also as pyromucic acid, was prepared as early as 1818. Houtou-Labillardière,[47] following the then prevailing custom of pyrolyzing solid compounds, distilled mucic acid and obtained considerable liquid and a solid crystalline compound (m.p. 130°), which he called "pyromucic acid." The presence of a carboxyl group causes furoic acid to exhibit[48] properties akin to those of aromatic compounds. It is brominated at 100°, nitrated by fuming nitric acid, and sulfonated by fuming sulfuric acid. The further action of nitric acid on the last two compounds yields dinitrofuran and nitrofuran sulfonic acid, respectively, by elimination of the carboxyl group.

Had the liquid, which accompanied the isolation of pyromucic acid, been examined carefully, it is possible that the discovery of *furan* would have antedated Faraday's preparation of benzene by 7 years. It was not until 1870, however, that this acid was decarboxylated[49] by pyrolysis

[47] HOUTOU-LABILLARDIÈRE, *Ann. chim. phys.* [2], **9**, 365 (1818).

[48] HILL and PALMER, *Am. Chem. J.*, **10**, 373 (1888); HILL and SYLVESTER, *ibid.*, **32**, 185 (1904); HILL and WHITE, *ibid.*, **27**, 193 (1902); KLINKHARDT, *J. prakt. Chem.*, [2] **25**, 41 (1882); PRIEBS, *Ber.*, **18**, 1362 (1885).

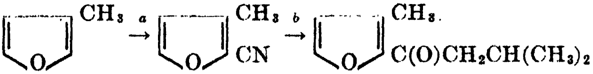
[49] LIMPRICHT, *ibid.*, **3**, 90 (1870).

of the barium salt with lime (nowadays we use quinoline and copper). At that time, pyromucic acid was suspected of belonging to the same series as salicylic acid. Although the new compound, which boiled at 32°, gave no color with ferric chloride, did not react with sodium, formed no acid with potassium and carbon dioxide, and gave a brownish-black amorphous mass with acids, the persistence of the original idea prompted the name "tetraphenol." A little later, Baeyer[50] recognized its true position and gave it the name furfuran, since shortened to furan, after the better known furfural.

5-*Bromofuroic acid* in the form of the ethyl ester participates in a most unusual reaction.[15] When treated with aluminum chloride and *n*-amyl chloride, *n*-hexyl bromide, or *n*-octadecyl bromide, the product is in each instance ethyl 5-bromo-4-*t*-butyl-2-furoate. In spite of the vigorous action needed for breaking a carbon-carbon bond, a yield as high as 46 per cent is obtained from octadecyl bromide.

Furan-β-carboxylic acid has been isolated from natural products such as *Euonymus atropurpureus Jacquin*, a shrub known in Northern and Western United States as "wahoo" or "burning bush" from the copious crimson-colored fruit. The powdered root bark or its alcoholic extract has some medicinal use similar to digitalis. The acid[51] is separated from the many other products as crystals in the residue left by steam distillation of the extract. The same compound has also been found[52] among the products from the roots of *Phaseolus multiflorus Lamarck*, commonly called the scarlet runner bean.

Elsholtzione is a ketone[53] obtained from the essential oils, recovered by steam distillation, of *Elshotzia cristata Willdenow*. Sodium and amyl nitrite convert it to isobutyraldoxime and ethyl elsholtzate (3-methylfuroic ester). Pyrolysis of the acid at 210 to 230° yields 3-methylfuran. The ketone is synthesized[54] by the sequence of steps pictured below. The acid can be made from the aldehyde by oxidation with silver oxide.



[a] A sequence of steps for introducing a nitrile group is (1) formation of an imine with HCN·HCl; (2) hydrolysis to aldehyde; (3) formation of an oxime with hydroxyl amine; (4) formation of a nitrile with acetic anhydride. [b] $BrMgCH_2CH(CH_3)_2$ followed by hydrolysis.

Because halogens give a variety of products with furan, the preparation of many *halogenated compounds* must be accomplished by bromination or chlorination of furoic acid followed by decarboxylation. Monohalogen compounds have a pleasant sweet odor somewhat resembling chloroform or bromoform. In general, the halogen is unreactive[55] to aqueous sodium hydroxide, sodium cyanide, dimethyl mercury, dimethylzinc, and sodium. α-Bromo- and α-iodo-furan form Grignard reagents with magnesium copper alloy; 2,5-diiodofuran yields 5-iodofurylmagnesium iodide; and β-iodofuran gives less than 1 per cent of furylpotassium with sodium-potassium alloy[56]; but the great majority of halogen compounds are not convertible to organometallic compounds. Halogen can be removed, however, by means of zinc dust and ammonia solution.[15]

---

[50] BAEYER, *ibid.*, **13**, 879 (1880).

[51] ROGERSON, *J. Chem. Soc.*, **101**, 1040 (1912); see also Ref. 13.

[52] POWER and SALWAY, *Pharm. J.*, **90**, 550 (1913); *C.A.*, **7**, 2659 (1913).

[53] ASAHINA and coworkers, *Acta Phytochim.* (*Japan*), **2**, 1 (1924); *C.A.*, **19**, 1139 (1925).

[54] REICHSTEIN, ZSCHOKKE, and GOERG, *Helv. Chim. Acta*, **14**, 1277 (1931).

The influence of the furyl radical on halogen reactivity may extend beyond the nucleus. α-Furfuryl chloride with magnesium yields some *sym*-difurylethane, probably through the intermediate Grignard reagent. 2-α-Furylethyl chloride[57] forms the reagent smoothly. γ-Furylpropyl chloride, on the other hand, gives negative results. The tetrahydro-derivative of the last[58] compound, however, gives the reagent in 92 per cent yield.

Sugars that have a furan system are called *furanosides*. Vitamin C is an α-ketofuranoside. The chemistry of these compounds, however, is largely concerned with the hydroxyl or aldehyde groups present.

Problems

1. If furan is so sensitive to the action of hydrochloric acid, how do you account for the formation of furfural by this reagent?

2. Give the products formed in the following reactions: (*a*) Acetonylacetone[59] distilled with anhydrous zinc chloride. (*b*) Methyl α,β-diacetylsuccinate[60] treated with mineral acid.

3. Suggest a method, (start with chloroacetone and acetonedicarboxylic ester) for the preparation of 2-cyano-4-methyl-3-furoic acid and from thence β-methylfuran.[61]

4. Outline steps that would lead from furoic acid to ethyl 5-acetamino-2-furoate and subsequently to ethyl 4-amino-5-acetamino-2-furoate,[35] and thence to 4-hydroxy-5-acetamino-2-furoate.

5. Furan and acetyl chloride, in the presence of tin tetrachloride, yield furyl methyl ketone. What is the shortest method of proving beyond doubt that substitution has occurred in the alpha position[24,35]?

6. Suggest a method for preparing furan-2,5-dicarboxylic acid.[24]

---

[55] Shepard, Winslow, and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930). See also Ref. 24.

[56] Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931); *J. Am. Chem. Soc.*, **55**, 2893 (1933).

[57] Amstutz and Plucker, *ibid.*, **63**, 206 (1941).

[58] Gilman and Hewlett, *Rec. trav. chim.*, **51**, 93 (1932).

[59] Dietrich and Paal, *Ber.*, **20**, 1085 (1887).

[60] Knorr and Cavallo, *ibid.*, **22**, 155 (1889).

[61] Rinkes, *Rec. trav. chim.* **50**, 1127 (1931); Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

7. How would you show that the two carboxyl groups of furan dicarboxylic acid are in the alpha positions?[24]

8. Since furfuryl chloride and sodium cyanide fail to form furfuryl nitrile, how would you proceed to synthesize furyl-acetic acid in order to prove its nonidentity with the hydrolysis product of cyanomethylfuran?[37]

9. Since *n*-, iso-, *sec*-, or *tert*-butyl chloride react with ethyl furoate and give a *tert*-butyl derivative,[15] how can the *n*-, iso-, or *sec*-butyl derivative be prepared?

10. What is the product of reaction of *tert*-butyl chloride with furyl phenyl ketone in the presence of aluminum chloride? Give a method for showing which ring has been substituted.[32]

11. Write reactions for the synthesis of δ-phenyllevulinic acid[26] from a furan compound.

12. Mercuric chloride, in the presence of sodium acetate, forms a mono- and a di-chloromercurifuran[18] from furan. How can you prove that the second radical is in an alpha position?

13. What are the probable compounds formed by the action of 2-chloromercurifuran with arsenic trichloride?[62]

14. Give the product formed from each of the following reactions: (*a*) 5-Methylfurfural refluxed with hydrazine hydrate in methyl alcoholic potassium hydroxide.[63] (*b*) *p*-Toluidine passed over aluminum oxide with furan at 450°.[30] (*c*) Ethyl furoate with hydrogen and Raney nickel catalyst at 150° and 100 to 135° atm. (*d*) Uncontrolled nitration of furoic acid or furoyl chloride.[64]

15. When dry bromine is allowed to stand at ordinary temperatures with furoic acid, a tetrabromo derivative is obtained. What product might be suspected? What would be the product of oxidation by dilute chromic acid?[65]

16. When bromine is passed over furoic acid at 100°, a monobromofuroic acid is obtained. The position of the bromine atom was originally shown by use of hot dilute nitric acid. What reaction occurred?[66]

17. How would you prepare 4-chloro-2,3,5-triphenylfuran and 2,3,5-triphenylfuran from benzil and acetophenone as starting materials?[67]

18. Fuming nitric acid is added dropwise to a solution of 2-furyl phenyl ketone in acetic anhydride at 0°. How would you show in what ring nitration has occurred?[33]

19. What is the product obtained by heating ethyl acetoacetate with potassium succinate in the presence of acetic anhydride? How would you convert the 4-carbethoxy group, formed in this reaction, to an amino group?[11]

20. Give the products formed from the action of α,β-dichloroethyl ether with ethyl acetoacetate under the influence of ammonia.[68]

21. In tests of the reaction with bromine, it has been found that furylacrylic acid,[20] furylethylene,[20] and furylmethyl ketone[24] give, respectively, substitution in the heterocyclic ring, addition to the ethylene linkage, and substitution in the methyl group. How would you prove the positions of the various bromine atoms?

22. How would you prepare furylacetylene from furylacrylic acid?[20]

---

[62] LOWE and HAMILTON, *J. Am. Chem. Soc.*, **57**, 1081 (1935).

[63] REICHSTEIN, *Helv. Chim. Acta*, **13**, 345 (1930).

[64] GILMAN and YOUNG, *Rec. trav. chim.*, **51**, 764 (1932).

[65] TÖNNIES, *Ber.*, **11**, 1085 (1888).

[66] HILL, *ibid.*, **16**, 1130 (1883); HILL and SANGER, *Ann.*, **232**, 46 (1886); see also Ref. 24.

[67] JAPP and KLINGEMANN, *J. Chem. Soc.*, **57**, 662, 674 (1890).

[68] BENARY, *Ber.*, **44**, 493 (1911); see also Ref. 11.

23. What compounds would be expected when ethyl acetoacetate reacts with chloroacetone under the influence of ammonia?[69] How would you proceed in successive steps[54] to obtain, from the primary furan product a 3-carboxy-2,4-dimethylfuran, a 2,4-dimethylfuran, and 3,5-dimethyl-2-furoic acid?[69]

24. What is the product of addition of maleic anhydride to 3-bromofuran? How would you convert the product to a phthalic acid or anhydride so that the position of the bromine atom in the original furan can be determined by reference to a known phthalic acid derivative?[70]

25. Furfural is condensed with nitromethane and the product $C_5H_5NO_3$ is treated with fuming hydrochloric acid for 10 min. The final product has the composition $C_6H_9NO_5$. Write equations for the reactions.[71]

---

[69] Feist, *ibid.*, **35**, 1545 (1902).

[70] Van Campen, Jr., and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

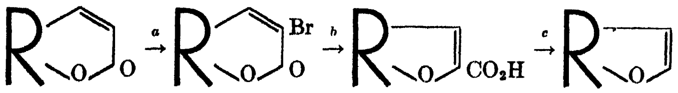
[71] Thiele and Landers, *Ann.*, **369**, 300 (1909).

CHAPTER II

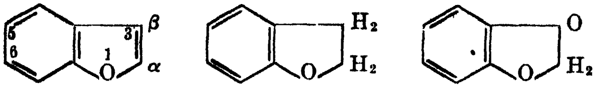
CONDENSED FURAN SYSTEMS

BENZOFURAN

Discovery and Naming.—While endeavoring to unravel the constitution of coumarin, Perkin[1] added bromine, treated the dibromide with alcoholic and then with aqueous alkali, and finally decarboxylated the product. Since all compounds in this sequence were derived from coumarin, they were named as derivatives of coumarin. The common name, coumarone, for the final product persists today, although partly supplanted by the term benzofuran, which is technically preferable because it is more descriptive of the series to which it belongs.



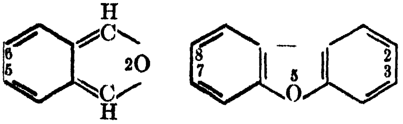
[a] (1) Addition of Br_2; (2) elimination of HBr by alc. KOH. [b] (1) Aqueous KOH opens ring and then forms a five-membered ring by elimination of HBr; (2) HX. [c] Pyrolysis of coumarilic acid. Large R signifies the benz system. This simplification will be used often in this text.



Benzofuran
Coumarone

Dihydrobenzofuran
Coumaran

Coumaran-3-one

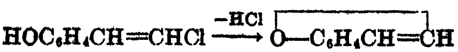


Isobenzofuran
Isocoumarone

Diphenylene oxide
Dibenzofuran

FIG. 1.—Naming and numbering of condensed furan systems.

Methods of Ring Closure.—The various syntheses are classified according to which of three bonds, the 1,3-, the 2,3-, or the 3-to ring, is formed. Union of the *first type* is frequently accomplished by elimination of hydrogen halide. A typical example is the formation of coumarilic acid from α-bromo-2-hydroxycinnamic acid, one of the steps described above. Similarly, o-hydroxystyryl chloride[2] yields coumarone.



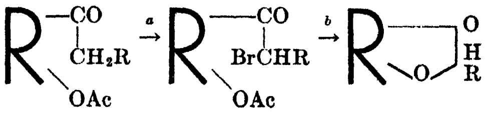
$$HOC_6H_4CH{=}CHCl \xrightarrow{-HCl} \overbrace{O{-}C_6H_4CH{=}CH}$$

---

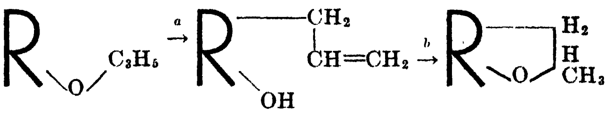
[1] PERKIN, *J. Chem. Soc.*, **8**, 368 (1870); **9**, 37 (1871).

[2] KOMPPA, *Ber.*, **26**, 2968 (1893).

The method is widely applicable. Coumaranones[3] are made by elimination of hydrogen bromide from a brominated acetophenone; coumarans are made from *o*-allylphenols, presumably by addition and elimination of hydrogen bromide. This last synthesis, originally discovered by Claisen,[4] is important for the preparation of compounds somewhat similar to vitamin E, a chroman compound. If the influence of the phenolic group is blocked by acylation, the addition of hydrogen bromide to the allyl system can be regulated so that with peroxide-free reagents a coumaran results, but with peroxide-containing mixtures a chroman, or six-membered ring, forms.[5] So readily do coumarans form that the heat necessary to effect rearrangement to the *o*-allylphenol in the above illustration will cause the formation also of some coumaran.[6]

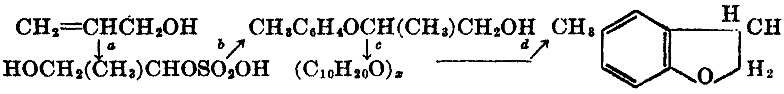


[a] Br_2 in CS_2. [b] Excess $CaCO_3$.



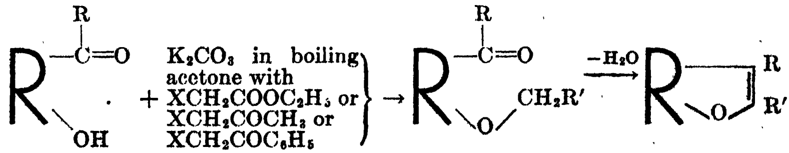
[a] Allyl phenyl ether (prepared from sodium phenoxide and allyl bromide in boiling acetone with potassium carbonate) heated in an atmosphere of carbon dioxide. [b] HBr or pyridine hydrochloride.

The reaction sometimes appears complex. For example, *p*-cresol, refluxed with allyl alcohol in sulfuric–glacial acetic acid solution, yields first a polymer, which then is pyrolyzed to the dihydrobenzofuran.[7]



[a] H_2SO_4. [b] p-$CH_3C_6H_4OK$. [c] Loss of water. [d] Pyrolysis of the polymer.

The *second method* of preparation, by formation of the 2,3-bond, begins with an aldehydo or keto phenol and progresses by way of a phenoxy derivative to the benzofuran. The necessary aldehyde is supplied by a



R = H, alkyl, or aryl. R′ = $COOC_2H_5$, $COCH_3$, COC_6H_5.

---

[3] Friedländer and Neudörfer, *ibid.*, **30**, 1077 (1897).

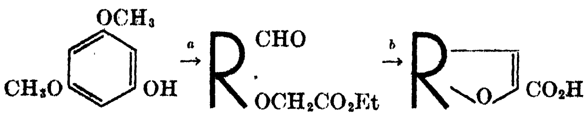
[4] Claisen and Tietze, *Ann.*, **449**, 81 (1926).

[5] Hurd and Hoffman, *J. Org. Chem.*, **5**, 212 (1940).

[6] Bartz, Miller, and Adams, *J. Am. Chem. Soc.*, **57**, 371 (1935).

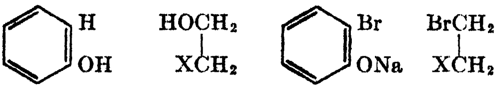
[7] Niederl and Storch, *ibid.*, **55**, 4549 (1933).

Gattermann synthesis ($HCN + HCl$); the ketone is made by a similar reaction known as Hoesch's method ($CH_3CN + HCl$), or by a conventional Friedel-Craft synthesis ($RCOCl + AlCl_3$). Introduction of these substituents occurs readily in phenols and more easily in resorcinol and phloroglucinol. Ring closure is then accomplished by (*a*) the familiar Perkin reaction, which yields a nonacidic coumarone because the carboxyl group is unstable, or (*b*) the familiar condensation of aldehydes with esters under the influence of alkali, which effects cyclization with retention of the carboxyl group. A typical example[8] of this synthesis is shown below.



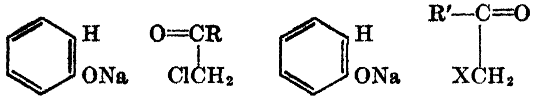
[a] $HCN + HCl$, $BrCH_2CO_2Et + K_2CO_3$ in boiling acetone. [b] Hydrolysis, $(CH_3CO)_2O + NaOAc$ or NaOEt in boiling alcohol. Large R = $(CH_3O)_2C_6H_2$.

The *third* general method depends on the formation of the bond between the aromatic ring and the 3-position as the final step. Reagents that can thus be used are shown in Fig. 2. The necessary phenoxy intermediate is prepared by refluxing an acetone solution of the phenol and halogen compound with potassium carbonate or by heating the two together in the presence of sodium ethoxide at 180–200°. Ring formation is then effected by the reagent indicated.



By zinc chloride(9)

By sodium(10)



R=H, alkyl, or aryl, By zinc chloride in acetic acid (11)

By $AlCl_3$ when R′=Cl(12)
By P_2O_5 when R′=OH(13)

FIG. 2.—Units for synthesis of compounds in the benzofuran series by formation of the 3- to ring link from a phenoxy intermediate. The agent for the ring closure is shown below each group.

[8] FOSTER and ROBERTSON, *J. Chem. Soc.*, 921 (1939).

[9] RINDFUSZ, *J. Am. Chem. Soc.*, **41**, 665 (1919); RINDFUSZ, GINNINGS, and HARNACK, *ibid.*, **42**, 157 (1920).

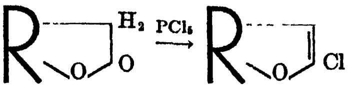
[10] STOERMER and GÖHL, *Ber.*, **36**, 2873 (1903).

[11] STOERMER, *Ann.*, **312**, 237 (1900).

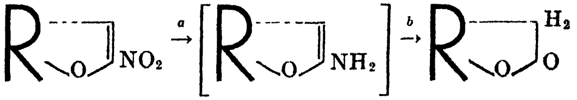
[12] STOERMER and ATENSTÄDT, *Ber.*, **35**, 3560 (1902).

[13] STOERMER and BARLACH, *ibid.*, **33**, 3175 (1900).

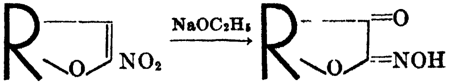
In addition to these general methods, any appropriate lactone can be converted to an α-chlorocoumarone[14] by phosphorus pentachloride.



Reaction of Benzofuran Compounds.—The chemical behavior of coumarones is, in general, that predicted for a furan system whose reactivity has been dampened by union with an aromatic nucleus. Acetic anhydride in the presence of tin tetrachloride, n-butyllithium,[15] or nitric acid introduces an acetyl, lithium, or nitro substituent, respectively, in the 2-position. Reduction[16] of the 2-nitro compound gives the lactone of o-hydroxyphenylacetic acid, a behavior reminiscent of some of the difficulties in the preparation of furyl amines. When the nitro compound is treated with sodium ethoxide, an intramolecular rearrangement produces isonitrosocoumaranon, the α-monoxime[17] of coumarandion.



[a] Sn + HCl. [b] H_2O.



Similar changes are noted among aromatic compounds,[18] *e.g.*, with α- and β-nitronaphthalene, 9-nitrophenanthrene, 9-nitroanthracene, and nitrostilbene.

Substitution takes place in either the benzene or the furan nucleus, depending on the substituents already present in the ring. A negative group in a furan ring favors substitution in the aromatic portion. Bromination or acylation of ethyl benzofuran-2-carboxylate, for example, yields a 5-bromo or 5-acetyl derivative, respectively. The methyl group in the β-position of 4,6-dimethoxy-3-methylbenzofuran facilitates the formation of an α-formyl product from the Gattermann synthesis (HCN and HCl). The methyl-free compound, on the other hand, produces the 7-formyl product in poor yield; the same compound with a carbethoxy group in the 2-position gives the 7-formyl compound[8] in good yield. The carboxyl or carbethoxy group is frequently used also to protect a position during a reaction and subsequently is eliminated.

---

[14] Stoermer, *Ann.*, **313**, 85 (1900).

[15] Smith, *Iowa State Coll. J. Sci.*, **12**, 155 (1937); *C.A.*, **32**, 2938 (1938).

[16] Stoermer and Kahlert, *Ber.*, **35**, 1640 (1902); Stoermer and Richter, *Ber.*, **30**, 2094 (1897).

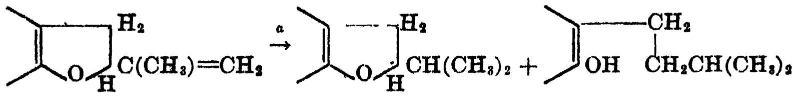
[17] Stoermer, *ibid.*, **45**, 163 (1912).

[18] Stoermer and Kahlert, *ibid.*, **35**, 1640 (1902).

Bromine or chlorine[19] add readily to benzofuran at the 2,3-positions. Alcoholic potash converts the dibromide to 3-bromocoumarone, but heat[20] produces the 2-bromo isomer.

Reduction by sodium and alcohol[21] or by catalytic hydrogen gives dihydrobenzofuran. Oxidation of the dihydro compound by chromic acid in acetic acid solution or less satisfactorily by lead tetraacetate[15] reforms the benzofuran. The furan system is reduced less readily than a carbonyl group because reduction (H_2 + Pt) of 2-acetobenzofuran affects the carbonyl and gives 2-(1-hydroxyethyl)-benzofuran.[22] By contrast, catalytic reduction of benzalacetone, which similarly has an α, β-unsaturated ketone structure, gives benzylacetone as the first step.[23] Reduction of the acetobenzofuran over Raney nickel is complete and gives 2-(1-hydroxyethyl) dihydrobenzofuran.

Other reductions, in which the oxygen atom participates, can occur. Tubaic acid (Fig. 3) is a dihydrobenzofuran compound with an unsaturated side chain in the alpha position. It undergoes a novel reduction with simultaneous ring opening, caused by the presence of an α,β-unsaturated ether, $-O-\overset{|}{C}H-\overset{|}{C}=CH_2$, which, according to Schopf,[24] is comparable to a conjugated diolefin system. In other words, the ethereal oxygen acts as a double bond and absorbs hydrogen. Hence, partial reduction gives a 1,2-addition compound, dihydrotubaic acid, and complete reduction gives tetrahydrotubaic acid as shown by partial formulas below. Certain codein derivatives also show a similar complete reduction with ring opening for the same reason.



a H_2 + PtO_2 at 48 lb.

Ozonization opens the ring.[25] Benzofuran, for example, yields about 25 per cent of *o*-hydroxybenzoic acid and 40 per cent of *o*-hydroxybenzaldehyde when thus treated. Alcoholic potassium hydroxide[26] at

---

[19] Fittig and Ebert, *Ann.*, **216**, 168 (1883).

[20] Stoermer and Kahlert, *Ber.*, **35**, 1633 (1902).

[21] Alexander, *ibid.*, **35**, 2409 (1902).

[22] Shriner and Anderson, *J. Am. Chem. Soc.*, **61**, 2705 (1939); **60**, 1415 (1938).

[23] Kern, Shriner, and Adams, *ibid.*, **47**, 1147 (1925).

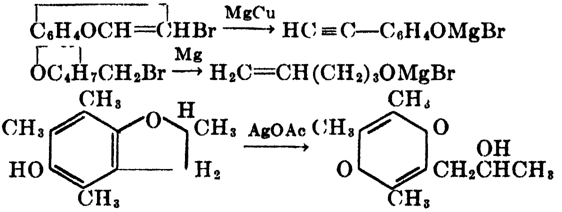
[24] Schöpf, *Ann.*, **452**, 237 (1927); Schöpf and Pfeifer, *ibid.*, **483**, 157 (1930).

[25] v. Wacek, Eppinger, and v. Bézard, *Ber.*, **73**, 521 (1940).

[26] Stoermer and Kahlert, *ibid.*, **34**, 1806 (1901); **35**, 1630 (1902).

200° also opens the ring, but concentrated ammonia[27] at 280° fails to do so.

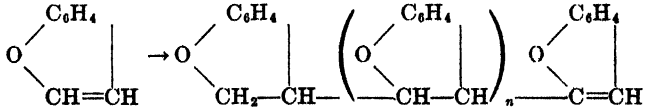
Substituents can facilitate ring opening and increase the variety of reagents employed. Warm aqueous alkali is sufficient to convert the oxygen-containing 3-coumaranone to *o*-hydroxyphenacyl alcohol.[3] Magnesium-copper alloy cleaves 3-bromobenzofuran[28] to *o*-ethinylphenol (17 per cent) in addition to forming the expected Grignard product. The reaction is somewhat analogous to that of the same reagent on tetrahydrofurfuryl bromide and is related to the general phenomenon of ether cleavage when metals react with *β*-halogen ethers. Mild oxidizing agents convert 5-hydroxycoumarans[29] to quinones. Hydriodic acid, followed by zinc dust and hydrochloric acid, opens the dihydrobenzofuran ring and forms *o*-ethylphenols.[30] Reference has been made in the previous section to the influence of a *β*-vinyl group in ring opening during hydrogenation.



$$C_6H_4OCH{=}CHBr \xrightarrow{MgCu} HC{\equiv}C{-}C_6H_4OMgBr$$

$$OC_4H_7CH_2Br \xrightarrow{Mg} H_2C{=}CH(CH_2)_3OMgBr$$

The extraordinary sensitivity of the furan system to acids is diminished in coumarone. Strong sulfuric acid (80 per cent and higher) induces formation of resins.[31] Indeed, this treatment, applied to the coal-tar fractions boiling from 168 to 175°C., gives the industrially important "cumar" or "paracumarone" resins. In practice,[32] a series of polymers ranging from the dimer to the octamer is obtained. The dimer is distilled (b.p. 335°/755 mm.) from the higher polymers and returned to the process. Polymerization is generally regarded as the result of the activity of an ethylenic system, such as is present in indene, rather than of the aldehyde-phenol product from ring opening. Distilla-



---

[27] Dohme, *Amer. Chem. J.*, **13**, 29 (1891).

[28] Reichstein and Baud, *Helv. Chim. Acta*, **20**, 892 (1937); Amstutz, *J. Org. Chem.*, **9**, 310 (1944).

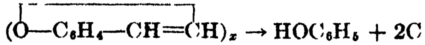
[29] Smith, Hoehn, and Whitney, *J. Am. Chem. Soc.*, **62**, 1863 (1940).

[30] Baeyer and Seuffert, *Ber.*, **34**, 52 (1901).

[31] Fittig, *Ann.*, **226**, 354 (1884); Kraemer, *Ber.*, **36**, 645 (1903); Kraemer and Spilker, *ibid.*, **23**, 81, (1890).

[32] Sheehan, Kelley, and Carmody, *Ind. Eng. Chem.*, **29**, 576 (1937).

tion of the resin regenerates the coumarone besides forming some phenol and other products of cracking. The latter change is pictured by the equation below.[11] Piperonylic acid pyrolyzes similarly to give carbon and the phenolic compound, protocatechuic acid.

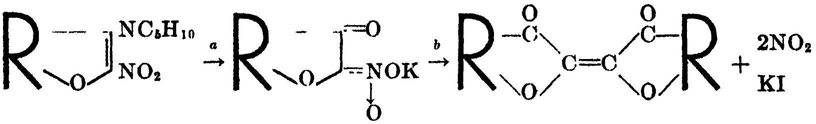


$$(\mathrm{O{-}C_6H_4{-}CH{=}CH})_x \rightarrow \mathrm{HOC_6H_5} + 2\mathrm{C}$$

Special Compounds.—*Coumarone* is a colorless oil,[33] which boils at 173 to 175° and has a specific gravity of 1.0705 at 25°. It is not frozen at −18°. It is insoluble in water and alkali and is volatile in steam and in ether. It can be identified by the melting points of its dibromide[34] (88 to 89°), picrate[34] (102 to 103°), and trinitrobenzene[35] addition compound (103.5 to 104°). Its monomethyl and dimethyl homologues[36] are found in higher boiling coal-tar fractions.

Coumarandione crystallizes in yellow plates that melt at 134°. It is obtained from *o*-hydroxyphenylglyoxylic acid and phosphorus pentoxide,[37] or from isatin by a sequence of treatments with sodium hydroxide, nitrous acid, sulfuric acid, and heat.[38] The β-carbonyl group behaves like an aldehyde and condenses readily with active methylene groups.

Oxindigo crystallizes in lemon yellow prisms (m.p. 276°). It is the oxygen analogue of indigo. It is made from 3-ethoxy- or 3-piperidino-2-nitrobenzofuran[39] as shown below, but has no practical value.



The starting material is prepared from the secondary amine and 2-nitro-3-bromocoumarone.
[a] KOEt. [b] I_2.

Coumaran-3-one, also called β-coumaranone and benzofuran-3-one, is obtained by heating *o*-hydroxychloroacetophenone with sodium acetate,[40] or by treating phenoxyacetic acid with phosphorus pentoxide.[13] This compound melts at 97°. An active methylene group is present. Hence aldehydes, ketones, and nitroso compounds react readily with β-coumaranone. In absolute alcohol in the presence of zinc chloride, benzaldehyde condenses in a 1:1 ratio to form an alkylidene derivative; in acetic acid in the presence of concentrated hydrochloric acid, it condenses in a 2:1 ratio to form a biscoumaranone dialkylmethane analogous to the product of a Knoevenagel reaction.[41] Synthesis of a typical alkylidene derivative[42] is shown below.

---

[33] Gennari, *Gazz. chim. ital.*, **24**, I, 470 (1890). Perkin, *J. Chem. Soc.*, **69**, 1201 (1896).

[34] Kraemer annd Spilker, *Ber.*, **23**, 78, 3276 (1890).

[35] Sudborough and Beard, *J. Chem. Soc.*, **99**, 209 (1911).

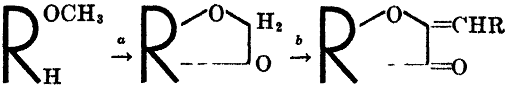
[36] Stoermer and Boes, *Ber.*, **33**, 3013 (1900).

[37] Fries and Pfaffendorf, *Ber.*, **45**, 154 (1912).

[38] (*a*) Baeyer and Fritsch, *ibid.*, **17**, 973 (1884); (*b*) Titoff, Müller, and Reichstein, *Helv. Chim. Acta*, **20**, 883 (1937).

[39] Stoermer and Brachmann, *Ber.*, **44**, 315 (1911).

[40] Fries and Finck, *ibid.*, **41**, 4271 (1908).

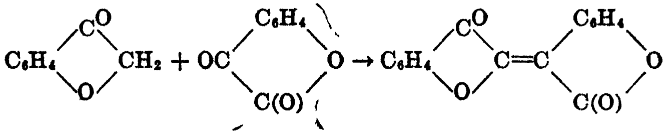


Large R = methoxybenz radical in which the methoxy group is para to oxygen; small R = an aromatic residue.

[a] $BrCH_2COCl + AlCl_3$ followed by heating with alcoholic sodium acetate. [b] $RCHO + ZnCl_2$.

The alkylidene shows variety in reduction.[42] With platinum, hydrogen selectively reduces the carbon-carbon double bond; with palladium on Norite, it reduces the carbonyl group also. The alkylidene compound reacts with bromine. Alcoholic sodium hydroxide may (*a*) eliminate hydrogen bromide from the dibromide and form a benzoylcoumaranone or (*b*) open the ring and then form a six-membered ring, a flavonol, by reaction with the other bromine atom. Ring opening is facilitated when methyl, methoxy, or chloro substituents are para to the oxygen atom in the coumaranone ring and is retarded when methyl or methoxy are in the meta position or two methoxy groups are in the benzylidene nucleus.[43] The benzoyl coumaranones can be distinguished from the isomeric flavonols by the fact that they have lower melting points, give no yellow color with blue fluorescence in concentrated sulfuric acid, and yield characteristic derivatives with diazonium salts.

Condensation of β-coumaranone with coumarandione gives *oxindirubin*.[44] The orange-yellow product melts at 215° and is the oxygen analogue of indirubin which is made by a similar reaction in the benzopyrrole series. See page 123.



Condensation with nitrosodimethylaniline gives an anil that condenses with another molecule of the coumaranone and forms *oxindigo*.[45]

---

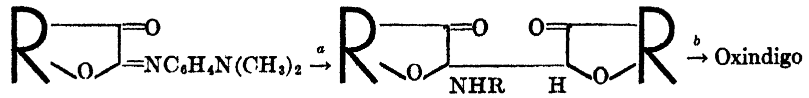
[41] Knoevenagel, *ibid.*, **31**, 2585 (1896). See also reference 42.

[42] Shriner and Damschroder, *J. Am. Chem. Soc.*, **60**, 894 (1938); Shriner and Anderson, *ibid.*, **60**, 1415 (1938).

[43] v. Auwers and Pohl, *Ann.*, **405**, 243 (1914).

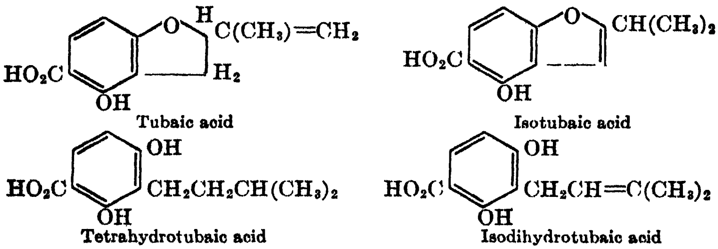
[44] Fries and Pfaffendorf, *Ber.*, **43**, 212 (1910); **44**, 114 (1911).

[45] Fries and Hasselbach, *ibid.*, **44**, 124 (1911).



Large R = C_6H_4; small R = $(CH_3)_2NC_6H_4$.
[a] Condensation of the anil with coumaranone. [b] HCl.

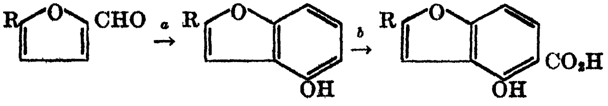
Tubaic acid, $C_{12}H_{12}O_4$, is an alkali cleavage product of rotenone,[46] one of the fish poisons (page 172). Determination of its structure was one of the important clues to the architecture of the parent compound. The formula shown in Fig. 3 accounts for (*a*) optical activity; (*b*) catalytic reduction of one double bond; (*c*) loss of a carboxyl group when heated and restoration of the carboxyl group by treatment of the product with alkali bicarbonates (Kolbe synthesis); and (*d*) presence of two oxygen atoms, one of which is indifferent to, while the other is reactive with, acylating and methylating (diazomethane) agents, the latter, however, with some difficulty. Drastic hydrogenation with palladium on Norite gives tetrahydrotubaic acid which (*a*) has no optical activity, (*b*) contains two phenolic hydroxyl groups, one of which is easily methylated, (*c*) forms a diacetyl derivative from which one acetyl group is removed readily by alcoholic potassium hydroxide, and (*d*) yields isocaproic acid when oxidized with permanganate.



Tubaic acid
Isotubaic acid
Tetrahydrotubaic acid
Isodihydrotubaic acid

FIG. 3. -Tubaic acid and related compounds.

Alkali fusion of tubaic acid gives isotubaic acid. In agreement with the properties of coumarones, isotubaic acid is not hydrogenated over platinum black so readily as is tubaic acid. The dihydro product, when obtained, is a racemic mixture that can be separated into enantiomorphs. The levo form is identical with dihydrotubaic acid. The compound is prepared[47] from a furfural homologue by a sequence of the Perkin and the Kolbe syntheses.



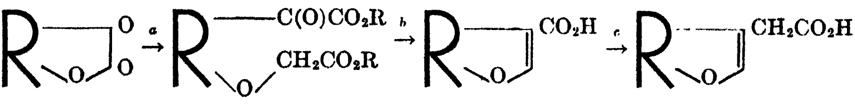
R = Isopropyl.
[a] Perkin condensation. Isopropylfurfural with sodium succinate and acetic anhydride at 140° for 35 hr. [b] Kolbe synthesis. Sodium salt and carbon dioxide.

---

[46] LaForge, Haller, and Smith, *Chem. Rev.*, **12**, 181 (1933).

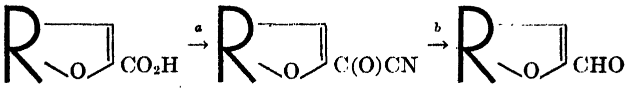
[47] Reichstein and Hirt, *Helv. Chim. Acta*, **16**, 121 (1933).

3-*Coumaronylacetic acid*[38b] has a structure similar to heteroauxin, the plant hormone (page 113), but without its activity. The synthesis, from coumarandione, contains some excellent examples of ring opening and closing, of relative stability of carboxyl groups, and of chain lengthening by the Arndt-Eistert reaction.



[a] NaOEt + $BrCH_2CO_2R$. [b] NaOEt. The 2,3-dicarboxylic acid product is heated to 270°. One carbon dioxide is lost. [c] $SOCl_2$ followed by CH_2N_2. The diazoketone is then treated with silver oxide and water. Arndt-Eistert synthesis.

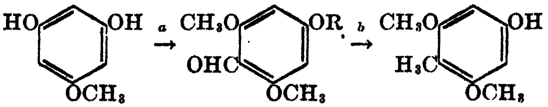
2-*Aldehydocoumarone* is prepared from 2-acetylcoumarone by oxidation with permanganate, or better from coumarilic acid[48] by a conventional series of steps for the preparation of aldehydes from acids.



[a] (1) $SOCl_2$; (2) HCN + pyridine. [b] (1) Hydrolysis. HCl + H_2O. (2) Decarboxylation of the glyoxylic acid in boiling aniline for 10 min.

Pyrousnic acid,[49] $C_{12}H_{12}O_5$ (m.p. 199 to 200°), is obtained by heating the optically active yellow lichen usnic acid, $C_{18}H_{16}O_7$, with 50 per cent aqueous sodium hydroxide in an atmosphere of hydrogen. Acetone is evolved. Diazomethane methylates only the single carboxyl group, but methyl iodide and potassium carbonate in boiling acetone methylates one carboxyl and two phenolic groups. Synthesis of this last acid from phloroglucinol occurs in three principal steps: (*A*) the introduction of a methyl group by reduction of the product of a Gattermann reaction, (*B*) the formation of a coumaran compound, and (*C*) the introduction of an acetic acid group, by use of an aldehyde-azlactone-oxidation sequence, a type of reaction that will be mentioned often in this text. The total series appears long, but the majority of the steps are chemical reactions that should be familiar to every organic chemist.

(*A*)

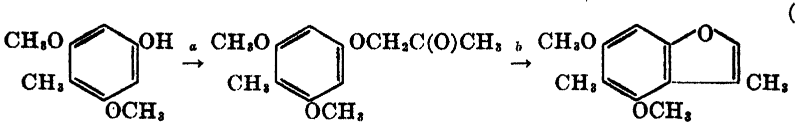


[a] (1) HCN + HCl; (2) $C_6H_5CH_2Br$ + K_2CO_3 in boiling acetone; (3) CH_3I + K_2CO_3. [b] H_2 + Pd on charcoal. The $C_6H_5CH_2$—, (R), is simultaneously eliminated. Introduction of the benzyl group permits differentiation of the ethers so that the desired phenolic group is obtained.

[48] Reichstein and Reichstein, *ibid.*, **18**, 1275 (1930).

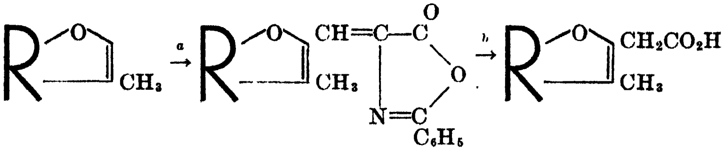
[49] Curd and Robertson, *J. Chem. Soc.*, 1173 (1933); Birch and Robertson, *ibid.*, 306 (1938).

(B)



[a] $ClCH_2C(O)CH_3 + K_2CO_3$ in boiling acetone. [b] H_2SO_4 below 0°.

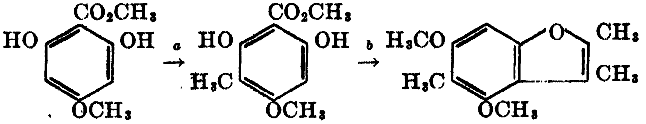
(C)



Large R = $CH_3(CH_3O)_2C_6H <$.

[a] (1) HCN + HCl to form aldehyde; (2) condensation of aldehyde with hippuric acid in the presence of sodium acetate and acetic anhydride to form an azlactone. [b] (1) Ring opening of the azlactone with 10 per cent NaOH to form a pyruvic acid. $-CH_2C(O)CO_2H$; (2) oxidation with H_2O_2.

Usenol,[50] $C_{11}H_{12}O_3$, (m.p. 178°) is derived from usnic acid by hydrolysis and thermal decomposition. It has a phenolic group, yields diacetyl and dibenzoyl derivatives, forms a dimethyl ether with methyl iodide and potassium carbonate in boiling acetone but not with diazomethane, and produces methylphloroacetophenone by ozone degradation. The probable structure, deduced from these facts, is confirmed by synthesis of the dimethyl ether from phloroglucinol. The steps are somewhat similar to those already described for synthesizing the dimethyl ether of pyrousnic acid.



The starting material is prepared from the methyl ester of phloroglucin carboxylic acid and diazomethane.

[a] (1) Saponification; (2) CH_3I + slight excess $NaOCH_3$; (3) Esterification with more $CH_3I + NaOCH_3$.

[b] (1) $CH_3CH(Cl)COCH_3 + K_2CO_3$; (2) $H_2O + HX$; (3) $-CO_2$; (4) $CH_3I + K_2CO_3$.

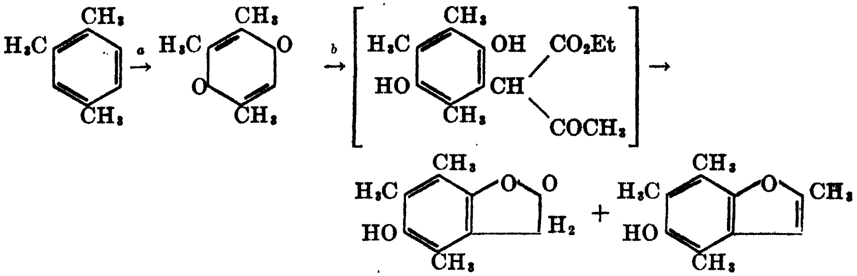
2,4,6,7-*Tetramethyl-5-hydroxycoumaran*[51] has the same substituents in the benz nucleus as are present in the aromatic portion of vitamin E. Indeed, the physiological properties and absorption spectra of many coumaran compounds are very similar to those in the chroman series. Synthesis of the corresponding coumarone begins with pseudocumene.[52] The initial steps are similar to some found in the preparation of certain chroman compounds. The products are the result of a 1,4-addition of

---

[50] CURD and ROBERTSON, *ibid.*, 714 (1933).

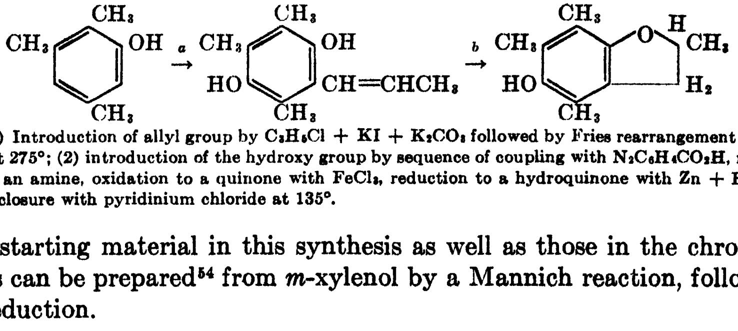
[51] SMITH, OPIE, WAWZONEK, and PRICHARD, *J. Org. Chem.*, **4**, 318 (1939).

[52] SMITH and MACMULLEN, *J. Am. Chem. Soc.*, **58**, 629 (1936).



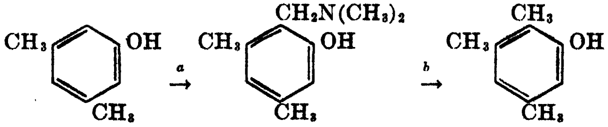
[a] (1) Br_2. The 5-bromo isomer forms also but can be made to change to the 3-bromo compound under influence of concentrated sulfuric acid, the Jacobsen reaction; (2) NaOH + Cu at 250–300°; (3) $Na_2Cr_2O_7$.
[b] NaOEt + $CH_3C(O)CH_2CO_2Et$.

the keto-ester to the conjugated bonds in the quinone, with subsequent ring closure and "acid" or "ketone" cleavage. 5-Hydroxy-2,4,6,7-tetramethylcoumarone and 5-hydroxy-4,6,7-trimethylcoumaranone are formed. Ethyl sodiomalonate yields the coumaranone only. Similar condensations occur with quinone itself. A direct synthesis[53] from 2,3,5-trimethylphenol is shown below.



[a] (1) Introduction of allyl group by C_3H_5Cl + KI + K_2CO_3 followed by Fries rearrangement of the ether at 275°; (2) introduction of the hydroxy group by sequence of coupling with $N_2C_6H_4CO_2H$, reduction to an amine, oxidation to a quinone with $FeCl_3$, reduction to a hydroquinone with Zn + HOAc.
[b] Ring closure with pyridinium chloride at 135°.

The starting material in this synthesis as well as those in the chroman series can be prepared[54] from *m*-xylenol by a Mannich reaction, followed by reduction.

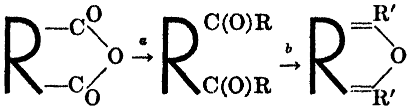


[a] Mannich reaction, H_2CO + $(CH_3)_2NH$. [b] H_2 at 177 atm. over Cu-Cr catalyst.

Isobenzofurans.—Isobenzofurans, with aromatic rings attached, can be prepared from appropriate diketones by reduction, or from phthaleins by action of sulfuric acid, or from dibenzoylethylene by the Diels-Alder synthesis. The first method is illustrated below by the preparation of a 1,3-diphenylisobenzofuran[55] from phthalic anhydride.

---

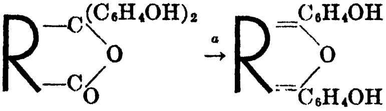
[53] SMITH, HOEHN, and WHITNEY, *ibid.*, **62**, 1863 (1940).
[54] CALDWELL and THOMPSON, *ibid.*, **61**, 765, 2354 (1939).
[55] BLICKE and PATELSKI, *ibid.*, **58**, 273, (1936).



Small R = $CH_3OC_6H_4-$. R′ = C_6H_4Cl which was derived from the anisyl radical in two steps by hydrolysis with hydrobromic acid and chlorination with phosphorus pentachloride.

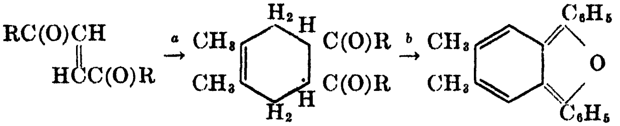
[a] $CH_3OC_6H_4MgBr$. [b] Reduction and elimination of water.

The second method[56] converts a phenolphthalein to an isobenzofuran. 9-Arylanthrone-10 may also form in this reaction by loss of water.



[a] H_2SO_4. Steps may include hydrolytic cleavage and recombination.

The third method[57] employs the diene synthesis as one of the steps of an interesting series that starts from *trans*dibenzoylethylene.[58]



[a] *Trans*dibenzoylethylene is made from maleic anhydride, benzene, and aluminum chloride. It condenses with dimethylbutadiene. [b] (1) H_3PO_4 in CH_3CO_2H gives a dihydroisobenzofuran; (2) conversion of the dihydroaromatic ring to an aromatic ring by addition of Br_2 followed by HBr elimination with NaOAc in HOAc, but the furan ring opens simultaneously; (3) reformation of furan ring by reduction with Zn + HOAc or Zn + NaOH in alcohol.

DIBENZOFURAN

Methods of Preparation.—When diphenyl ether is passed through a hot tube, diphenylene oxide is formed. The reaction is akin to the well-known formation of diphenyl from benzene, except that the hydrogen evolved forms phenol and benzene with another molecule of the ether.

$$2C_6H_5OC_6H_5 \rightarrow \overline{C_6H_4OC_6H_4} + C_6H_5OH + C_6H_6$$

Other methods of preparation are (*a*) dehydration of phenol over strongly heated thorium oxide; (*b*) pyrolysis of phenol over litharge (20 per cent yield)[59] for 8 hr. at 150°; (*c*) distillation of phosphoric acid esters over lime; and (*d*) diazotization of *o*-aminophenyl ethers. This last method is often used to locate the position of a substituent. For example, proof that nitration of diphenylene oxide occurs at C_3 is given by ring closure of an amino diphenyl ether[59] and conversion to a compound derived from the nitrated diphenylene oxide (see Fig. 4).

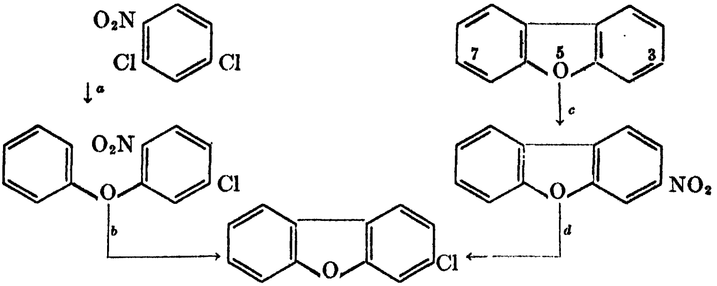
---

[56] Blicke and Patelki, *ibid.*, **58**, 559 (1936).

[57] Adams and Gold, *ibid.*, **62**, 56 (1940).

[58] Lutz, *ibid.*, **52**, 3423 (1930).

[59] Cullinane, *J. Chem. Soc.*, 2267 (1930).

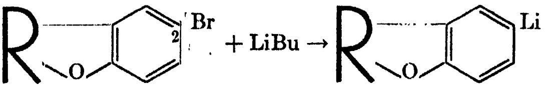


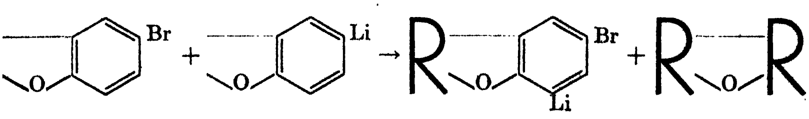
[a] C_6H_5OK. [b] $Fe + H_2O + FeCl_3$, HNO_2, H_2SO_4. [c] HNO_3. [d] $Sn + HCl$, $HNO_2 + CuCl$.

FIG. 4.—Synthesis of substituted diphenylene oxide compounds and proof of position of nitration.

Reactions of Diphenylene Oxide.—Replacement reactions are unique in that the position of the entering group is largely determined by the nature of the reactant,[60] not by any orientation by groups. Nitration, as already indicated, introduces a group in the 3-position. Halogenation and sulfonation, on the other hand, introduce their groups in the 2-position. Substitution in the 4-position occurs with mercuric acetate, methylthium, butylsodium, or sodium-potassium alloy. Excess of these metalating reagents leads to 4-6 disubstituted products.

Lithium can be introduced into the 2-position by interchange[61] of halogen and metal. A secondary reaction, caused by metalation at C_4 in the bromodiphenylene oxide by the new lithium compound, occurs in this process. The interchange of bromine and lithium is general. Eight different bromomethoxydibenzofurans[62] exchange their bromine atoms for lithium when treated with butyllithium.





Metallic compounds are valuable as intermediates for other products. The alkali metal derivatives undergo the usual reactions[63] with dimethylsulfate, carbon dioxide, iodine, sulfur dioxide, or oxygen (air). Mercurated products will yield iodo derivatives with iodine.

---

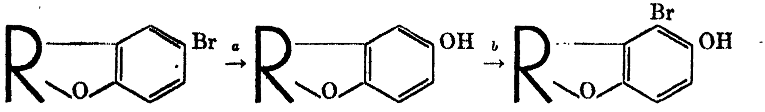
[60] GILMAN and YOUNG, *J. Am. Chem. Soc.*, **56**, 1415 (1934).

[61] GILMAN, CHENEY, and WILLIS, *ibid.*, **61**, 951 (1939); GILMAN, LANGHAM, and WILLIS, *ibid.*, **62**, 346 (1940).

[62] GILMAN, SWISLOWSKY, and BROWN, *ibid.*, **62**, 348 (1940).

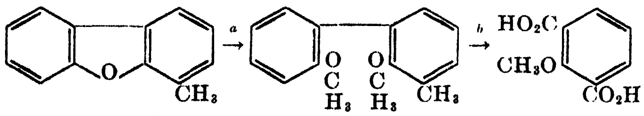
[63] GILMAN and YOUNG, *ibid.*, **57**, 1121 (1935).

Compounds with substituents in the 1-position are obtained either by synthesis or by indirect means.[64] A hydroxy group at C_2, for example, will direct a bromine to the 1-position, and a 2-methoxy group will direct lithium (from butyllithium) largely to the 1-position (4 parts at C_1 and 1 part at C_3). The orienting influence of the methoxy group is, therefore, greater than that of the ether link inside the ring.[65]



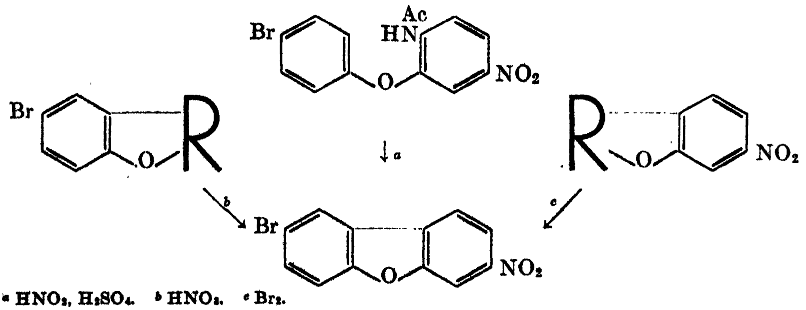
[a] $NaOH + CuSO_4 + Cu$ at 240° for 12 hr. [b] Br_2 in CH_3CO_2H.

Alkali fusion opens the ring.[66] The process is useful in structure determination, as, for example, in the case of a coal-tar constituent shown below.



[a] (1) Alkali fusion, (2) Me_2SO_4. [b] $KMnO_4$.

Influence of Substituents.—Substituents have an effect expected from their behavior in aromatic compounds. For example, a nitro group in the 3-position of dibenzofuran protects that ring from attack by another reagent and does not affect the position taken by a nitro or bromo group when it enters the other benz ring. Bromination[67] of 3-nitrodibenzofuran inserts a bromine atom in the other ring. The product is identical with that obtained by nitration of 2-bromodibenzofuran. The structure of the product is proved by synthesis. An amino group in one ring, however, facilitates the attack by other reagents in



[a] HNO_3, H_2SO_4. [b] HNO_3. [c] Br_2.
Large R = C_6H_4.

---

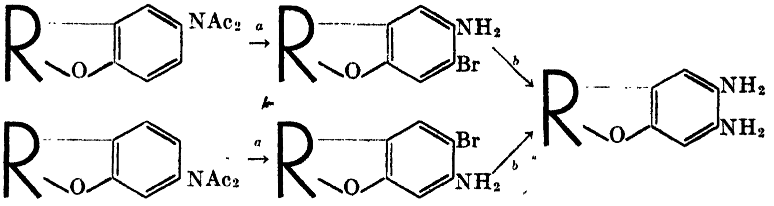
[64] GILMAN and VAN ESS, *ibid.*, **61**, 1365 (1939).

[65] GILMAN and BEBB, *ibid.*, **61**, 109 (1939).

[66] KRUBER, *Ber.*, **65**, 1382 (1932).

[67] MCCOMBIE, MACMULLAN, and SCARBOROUGH, *J. Chem. Soc.*, 529 (1931); CULLINANE, DAVEY an PADFIELD, *J. Chem. Soc.*, 716 (1934).

that same ring, exactly as it does in the aromatic series. Bromination of either 2- or 3-acetaminodibenzofuran introduces a halogen atom ortho to the amino group.[68] Proof of the position is given by conversion (CuBr and NH_4OH) of each bromoamino compound to the same diamino derivative, identified by formation of a quinoxaline (page 502) derivative with benzil or phenanthraquinone.



[a] Br_2, conc. HCl in EtOH. [b] CuCl + NH_4OH.

Reduction by sodium and absolute[69] alcohol or by catalytic (Pt black) hydrogen[70] yields 1,2,3,4-tetrahydrodibenzofuran (b.p. 268 to 269°). Addition of metalic sodium[71] in liquid ammonia gives 1,4-dihydrodibenzofuran. Permanganate (5 per cent)[71] solution, sulfur, or selenium restores the dibenzofuran. Phenyllithium[71] will dehydrogenate the dihydro compound also.

Physiological Properties.—The dibenzofuran nucleus is present in morphine (page 317). Hence the physiological properties[72] of compounds in this series are of considerable interest. Dibenzofuran itself has a little activity, as does also phenanthrene, which can similarly be carved from the morphine molecule. A mild depressant action results from the introduction of simple groups such as acetyl or propionyl. 2-Acetyldibenzofuran is readily converted to an aminoketone by (*a*) reduction of an isonitroso derivative, or (*b*) reaction of the bromo derivative with an amine. Catalytic reduction converts the ketone to an amino alcohol.

Brazan (m.p. 202°) is derived from brazilin (a pyrane compound) by distillation of some derivatives over zinc dust.[73] A possible synthesis[73] is effected by condensing 2,3-dichloro-α-naphthoquinone with resorcinol and subjecting the product to zinc-dust distillation. This structure is not regarded as settled.[74]

---

[68] Gilman, Brown, Bywater, and Kirkpatrick, *J. Am. Chem. Soc.*, **56**, 2473 (1934).

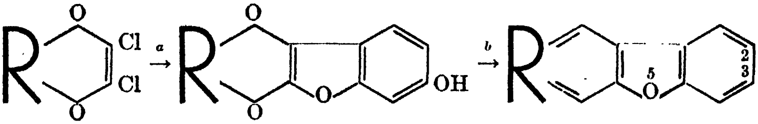
[69] Honigschmid, *Monatsh.*, **23**, 829 (1902).

[70] Cullinane and Padfield, *J. Chem. Soc.*, 1131 (1935).

[71] Gilman and Bradley, *J. Am. Chem. Soc.*, **60**, 2333 (1938).

[72] Mosettig and Robinson, *ibid.*, **57**, 902, 2186 (1935); Kirkpatrick and Parker, *ibid.*, **57**, 1123 (1935); Cook and Gilman, *Proc. Iowa Acad. Sci.*, **46**, 220 (1939); *C.A.*, **34**, 6941 (1940).

[73] v. Kostanecki and Lloyd, *Ber.*, **36**, 2193 (1903); Grafmann and v. Kostanecki, *ibid.*, **42**, 822 (1909); Perkin, Jr., and Robinson, *J. Chem. Soc.*, **95**, 381 (1909).



a Resorcinol + NaOEt. b Zn dust distillation.

Problems

1. Name each product that should be formed in the following cases: (*a*) The dry sodium salt of salicyl aldehyde is suspended in benzene and allowed to react with chloroacetone.[75] (*b*) The acetyl derivative of *o*-allylphenol is treated with bromine in carbon disulfide and the resulting dibromide is refluxed with an excess of alcoholic potash or sodium alkoxide.[76] How would you show that the product of this last reaction is not a chromene (six-membered ring) compound? Could the product of the reaction have been different if one equivalent of alcoholic potash had been used? (*c*) An acetone solution of 1 mole of phenol is refluxed on a steam bath with 1.1 mole each of potassium carbonate and 2-methylallyl chloride; the product of the first step is put in a flask and heated with or without a solvent (dimethylaniline) to 245°; and the principal product from the second step is heated with pyridine hydrochloride (bath temperature 235 to 245°) to form one product, or is added drop by drop to an aqueous solution of mercuric chloride, which is mechanically stirred,[6] to form another product. (*d*) Toluylquinone, ethyl acetoacetate, and zinc chloride are warmed together in acetone solution until a vigorous reaction is completed.[77] (*e*) Ethyl α-chloroacetoacetate, 33 g., is heated on a water bath with 25 g. of orcinol (5-methylresorcinol) in a concentrated solution of 4.6 g. of sodium in alcohol until the mixture is neutral.[78]

2. Describe the steps for preparing 4-hydroxycoumaran-3-one from resorcinol.[79] What is the product of the reaction of this heterocyclic compound with benzoyl chloride in the presence of sodium carbonate and water? In what way might the physical properties of the coumaranone differ from those of its 6- or 7-hydroxy isomer?

3. Devise a sequence of reactions for preparing 4,6-dimethoxy-3,5-dimethylcoumarone-2-carboxylic acid from phloroglucinol.[49]

4. 4-Hydroxy-coumarone-5-carboxylic acid[80] is derived from elliptone, one of the other constituents in the resin from the *Derris elliptica* root, a source of rotenone. It is formed by a cleavage similar to that which yields isotubaic acid from rotenone. Devise a method for its synthesis in the laboratory.

5. Write the equation for the preparation of 6-methoxycoumaran-3-one. How does a solution of the compound in glacial acetic acid react with acetone in the presence of some zinc chloride? How can the second product be converted to a 2-alkylcoumaranone or to an alkylcoumarane compound?[22]

---

[74] Ebel, *Helv. Chim. Acta*, **12**, 3 (1929).

[75] Stoermer, *Ber.*, **30**, 1711 (1897).

[76] Adams and Rindfusz, *J. Am. Chem. Soc.*, **41**, 648 (1919).

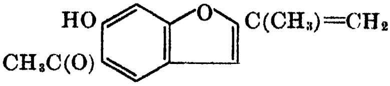
[77] Graebe and Levy, *Ann.*, **283**, 245 (1894).

[78] v. Kostanecki and Tambor, *Ber.*, **42**, 901 (1909); **29**, 237 (1896).

[79] Shriner and Witte, *J. Am. Chem. Soc.*, **61**, 2328 (1939).

[80] Harper, *J. Chem. Soc.*, 1424 (1939).

6. Euparin, a yellow crystalline material from the roots of *Eupatorium purpureum*, was suspected of containing a C-acetyl group



because the carbonyl group was resistant to reduction by hydrogen and a palladium catalyst and was unaffected by boiling 30 per cent alcoholic sodium hydroxide. How can the acetyl be replaced by an amino group and thus prove that there is a C-acetyl group present? What are the products of ozonalysis of a compound of the above formula?[81]

7. What is the product from each of the following reactions? (*a*) 2-Allyl-3,5,6-trimethylhydroquinone with a halogen acid.[82] (*b*) A mixture of thymol, benzoin, and 73 per cent sulfuric acid, heated to 150 to 170°.[83]

8. What is the product that results from the sequence of (*a*) allyl alcohol refluxed with *m*-cresol in sulfuric–glacial acetic acid; (*b*) precipitation with water; (*c*) distillation? Write the products for the same sequence of steps in a reaction between phenol and cinnamyl alcohol.[7]

9. Write the equation for preparing the 2-methylallyl ether of phenol and for the product obtained by heating the ether in a metal bath at 245°.[6]

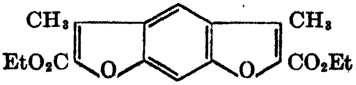
10. Devise a method for the preparation of (*a*) 2-acetobenzofuran from salicylaldehyde;[22] (*b*) α-benzoylcoumarone[78] from nonheterocyclic compounds.

11. A sequence of chemical changes converts 2,3,5-trimethylphenol to $C_{12}H_{16}O_2$.[53] Write the formula and name the product obtained in each step of the process when the reagents are: (*a*) the diazonium solution from sulfanilic acid; (*b*) sodium hydrosulfite; (*c*) formic acid; (*d*) sodium ethoxide and allyl chloride; (*e*) refluxing in kerosene at 225° for 7 hr.; (*f*) refluxing with 40 per cent hydrobromic acid for 2 hr.; (*g*) ferric chloride and hydrochloric acid in the cold; (*h*) refluxing with acetic anhydride, sodium acetate, and zinc dust; (*i*) refluxing with hydrobromic acid.

What would be the product that would result from the addition of ferric chloride and hydrochloric acid during a steam distillation of the product from (*b*)?

12. Show a method for the preparation of 5-nitro-2-aminophenol and write the products that result from a sequence of reactions which begins with that compound and uses in turn (*a*) nitrous acid followed by cuprous chloride, (*b*) methylation, (*c*) stannous chloride, (*d*) nitrous acid followed by 50 per cent sulfuric acid, (*e*) dimethylsulfate, (*f*) chloroacetyl chloride and aluminum chloride, (*g*) boiling alcohol containing sodium acetate, (*h*) benzaldehyde, (*i*) chlorine.[43]

13. Devise methods for the preparation of the following: (*a*) 4,6-, 2,5-, 2,6-, and 3,6-Dimethylcoumarone[11] from readily available phenolic compounds. (*b*) β-Naphthofuran from β-naphthol by way of β-naphthol aldehyde or by some other method.[11] (*c*) Bis(2-benzofuryl) ketone, $(-OC_6H_4CH{=}C-)_2CO$, from salicylaldehyde. (*d*) A difuran compound that has the structure[84]



---

[81] KAMTHONG and ROBERTSON, *J. Chem. Soc.*, 925 (1939).

[82] SMITH, UNGNADE, HOEHN, and WAWZONEK, *J. Org. Chem.*, **4**, 305 (1939).

[83] JAPP and MELDRUM, *J. Chem. Soc.*, **75**, 1035 (1899).

[84] HANTZSCH, *Ber.*, **19**, 2927 (1886).

14. What are the reactions of the following coumarone compounds with the agents indicated? (*a*) Coumaran-3-one with methylmagnesium iodide.[85] (*b*) 2-Bromocoumarone with sodium ethoxide in a closed tube at 200°; the same reaction with 3-chlorocoumarone.[11] (*c*) 2,3-Dichlorocoumaran with alcoholic potash.[11] (*d*) 5-Methylcoumaranone condensed with itself.[44,86] (*e*) Coumarone heated at 200° in a copper autoclave with alcoholic potassium hydroxide.

15. Describe a method for obtaining *o*-hydroxybenzoylformic acid from a heterocyclic compound.[16]

16. Devise a method which will prove that nitration occurs in the 2-position of coumarone.[87]

17. What is the final product into which 3,5-dimethyl-2-ethyl-phenol is converted after a sequence of reactions with (*a*) nitrous acid, (*b*) hydrochloric acid and hydrogen peroxide, (*c*) zinc and acetic acid, (*d*) allyl bromide and zinc chloride in benzene solution?[88]

18. Write the products that are formed when (*a*) hydroquinone dimethyl ether is treated with α-bromo-β-phenylpropionyl chloride in the presence of aluminum chloride in carbon disulfide in the cold, (*b*) the mixture is refluxed gently in an oil bath, and the product is then treated with alcoholic sodium acetate.[42]

19. What compound results when 2-chlorocyclohexanone is added dropwise to ethyl sodioacetoacetate in toluene and the product is heated with thirty times the quantity of 15 per cent hydrochloric acid for 10 hr.?[89]

20. What product results when *p*-chlorophenol is passed through a silica tube heated to dull redness?[90]

21. Propose a method for the synthesis of 2-bromodibenzofuran-6-carboxylic acid from nonheterocyclic materials.[91]

22. Direct iodination of dibenzofuran is impossible. How might 2,8-diiododibenzofuran be prepared indirectly?[92]

23. Bromination followed by conversion to the Grignard reagent and carbonation gives a diphenyleneoxide carboxylic acid probably in the 2-position. Suggest a synthesis from a nonheterocyclic compound that will show the position occupied by the carboxyl group.[93]

24. Substitution in the 2-position occurs when chlorosulfonic acid is dropped in a chloroform solution of dibenzofuran at 25°. Suggest a method for converting the sulfonic acid to the known iodo and carboxyl derivatives[92] in order to prove its position.

---

[85] STOERMER and BARTHELMES, *ibid.*, **48**, 62 (1915).

[86] BAKER and BANKS, *J. Chem. Soc.*, 279 (1939).

[87] STOERMER and KAHLERT, *Ber.*, **35**, 1640 (1902).

[88] KARRER and HOFFMANN, *Helv. Chim. Acta*, **22**, 654 (1939).

[89] EBEL, HUBER, and BRUNNER, *ibid.*, **12**, 16 (1929).

[90] BELL, *J. Chem. Soc.*, 1244 (1936).

[91] GILMAN, VAN ESS, and HAYES, *J. Am. Chem. Soc.*, **61**, 643 (1939).

[92] GILMAN, SMITH, and OATFIELD, *ibid.*, **56**, 1412 (1934).

[93] MEYER and KRIEGER, *Ber.*, **55**, 1659 (1922).

CHAPTER III

THIOPHENE AND CONDENSED THIOPHENE SYSTEMS

THIOPHENE COMPOUNDS[1]

Historical.—In 1879, A. Baeyer,[2] at work with derivatives of benzene, observed that the yellow solution of isatin in sulfuric acid first turned green and then an intense blue when shaken with supposedly pure benzene from coal tar. From a carbon and hydrogen analysis (no test for sulfur was made at that time), he concluded that the blue precipitate was a compound of the indole derivative and "phenol" (benzene). Hence the name "indophenin," by which this reaction became known. The test was used by Victor Meyer[3] as a lecture demonstration to show that a sample of benzene, prepared by pyrolysis of a mixture of sodium benzoate and soda lime was, indeed, benzene. To his amazement, the test failed. On the same day, he set to work to discover the cause of the abnormality and in 1882[4] reported that benzene, repeatedly shaken with concentrated sulfuric acid until no further color developed, gave the indophenine test with difficulty, but that "benzene" recovered from the sulfuric acid layer, by formation of the barium salt and distillation over sulfuric acid, gave the color readily. A year later,[4] with some help from an industrial company, he obtained a sufficient quantity (140 g. as the result of shaking 250 l. of benzene with 25 l. of concentrated acid, forming the lead salt, distilling with dry ammonium chloride, and then repeating these processes with ligroin as a solvent during sulfonation) to determine with surety its boiling point, 84°, to make analyses of the carbon, hydrogen, and sulfur, and to prepare and analyze the dibromo derivative. At his solicitation, the original indophenine compound of Baeyer was tested for sulfur and a corrected composition and analysis published.[5] Subsequently, with as much as 1,944 g. of pure thiophene from 2,000 l. of benzene, he carried through a series of studies on the properties of this material.

Isolation of Thiophene.—Sulfuric acid remains one of the important agents for isolating thiophene. Its use depends on the fact that the α-hydrogen atom of the heterocyclic compound is much more reactive than any attached to benzene. All other methods depend on this same differential. For example, mercuric oxide and acetic acid form the precipitate[6] $HOHg{\cdot}C_4H_2S{\cdot}HgO_2CCH_3$ from which the thiophene is recovered by distillation over moderately concentrated hydrochloric acid.

---

[1] STEINKOPF, "Die chemie des thiophen," Dresden und Leipzig, 1946.

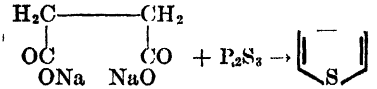
[2] BAEYER, *Ber.*, **12**, 1309 (1879).

[3] MEYER, "Die Thiophengruppe," Brunswick, 1888.

[4] MEYER, *Ber.*, **15**, 2893 (1882); **16**, 1465 (1883).

[5] MEYER, *ibid.*, **17**, 2641 (1884).

Preparation of Thiophene Compounds.—Methods of synthesis may be divided into two classes: (*a*) those which join sulfur to a series of four carbon atoms and (*b*) those which unite sulfur with smaller fragments such as acetylene or ethylene. An example of the first method is given by the reaction of sodium succinate with phosphorus trisulfide.[7] Any



diketone, ketoacid, anhydride, or sodium salt, which can theoretically change to a 1,4-dienol system, will produce a thiophene compound when heated with phosphorus tri- or penta-sulfide. Typical[8] of this class are acetonylacetone, levulinic acid, succinaldehyde, and succinic anhydride. These compounds are, in general, the same as those used for some of the syntheses in the furan series; although in the case of thiophene products, no thiol substituent remains on the nucleus. For example, levulinic acid yields methylthiophene rather than methylthiolthiophene. A carboxyl group, however, can remain attached as illustrated by the formation of α-thiophenecarboxylic acid when mucic acid is heated with barium sulfide at 200 to 210°.[9]

Dienes also form thiophene compounds with sulfur. Isoprene, for example, gives a 47 per cent yield of 3-methylthiophene[10] when passed through boiling sulfur at 350°. Furan compounds that have a diene-like behavior will yield the corresponding thiophene by passage over heated aluminum oxide with hydrogen sulfide.[11]

The second general method consists of uniting sulfur with ethylene or acetylene at high temperature. When passed through boiling sulfur in the presence of a special nickel catalyst, acetylene yields 40 per cent thiophene[12]; over pyrites at 420 to 600° or bauxite with hydrogen sulfide, these gases also give thiophene.[13]

---

[6] Volhard, *Ann.*, **267**, 172 (1892); Steinkopf and Bauermeister, *ibid.*, **403**, 50 (1914); Dimroth, *Ber.*, **32**, 758 (1899).

[7] Phillips, *Org. Syntheses*, **12**, 72 (1932); Coll. vol. II, 578.

[8] Volhard and Erdmann, *Ber.*, **18**, 454 (1885).

[9] Paal and Tafel, *ibid.*, **18**, 456 (1885).

[10] Shepard, Henne, and Midgley, Jr., *J. Am. Chem. Soc.*, **56**, 1355 (1934).

[11] Jurjew and Rakitin, *Ber.*, **69**, 2492 (1936).

[12] Broun, *J. Applied Chem.* (*U.S.S.R.*), **6**, 262 (1933); *C.A.*, **28**, 2710 (1934).

[13] Schneider, Boch, and Häusser, *Ber.*, **70**, 425 (1933); Stuer and Grob, U.S.P. 1,421,743; *C.A.*, **16**, 3093 (1922).

Physical Properties.—The nearness in boiling points of benzene and thiophene, which accounted for the presence of the latter in the indophenine test, is shown also by derivatives of these compounds.[14] The melting points of the members of the two series frequently show the same similarity (Table I), although the parent members and some derivatives such as the nitro- melt at widely separated values. As would be expected, thiophene has a higher specific gravity than benzene (1.0884 as compared with 0.8794). The sulfur compounds have also an electric moment (Table II).

TABLE I.—COMPARISON OF BOILING AND MELTING POINTS OF α-SUBSTITUTED THIOPHENE COMPOUNDS WITH CORRESPONDING COMPOUNDS IN THE AROMATIC SERIES

Thiophene series	B.p., °C.	M.p., °C.	Benzene series	B.p., °C.	M.p., °C.
Thiophene	84	−40	Benzene	80.09	5.51
Methylthiophene	113	.....	Toluene	110 3	−95
Ethylthiophene	132.4	.....	Ethylbenzene	136.15	−93.9
Propylthiophene	.....	.....	Propylbenzene	159.45	−101.6
Dithienyl	266	83	Diphenyl	254–255	69.71
Chlorothiophene	130	.....	Chlorobenzene	132	−45
Bromothiophene	150	.....	Bromobenzene	155	−30.6
Iodothiophene	182	.....	Iodobenzene	188.6	−31.4
Nitrothiophene	225	46.5	Nitrobenzene	210.9	5.7
Thiophenecarboxylic acid	260	126	Benzoic acid	249	122
Methyl thiophenecarboxylate	.....	.....	Methylbenzoate	199.6	−12.5
Thiophene nitrile	190	.....	Benzonitrile	190.7	−13
Methyl thienyl ketone	213.5	9	Acetophenone	202.3	19.7
Benzoylthiophene	326	.....	Benzophenone	306	49
Thienylacrylic acid	.....	138	Cinnamic acid	.....	133
Thionylacetic acid	.....	76	Phenylacetic acid	265.5	76.7
Thienylmercuric chloride	.....	.....	Phenylmercuric chloride		

Crystallographic data measured at −170° likewise show the following relationship.

Benzene: Orthorhombic system $a = 7.34 \quad b = 9.52 \quad c = 6.74$
$V = 471 \times 10^{-24}\ \text{cm.}^3 \quad D = 1.099$
Thiophene: Tetragonal system $a = 7.22 \quad e = 9.54$
$V = 498 \times 10^{-24}\ \text{cm.}^3 \quad D = 1.11$

This close relationship is probably caused[14] by a similarity in the outer electron systems of sulfur and of the double methine group, —HC═CH—. The latter behaves, therefore, as a pseudo sulfur atom. The fact that resonance potentials of sulfur and acetylene are the same,

---

[14] ERLENMEYER and LEO, *Helv. Chim. Acta*, **16**, 1381 (1933).

6 volts, while that of oxygen is 9.1 volts, probably accounts for the fact that benzene and thiophene compounds are so frequently alike and so different from the furans.

TABLE II.—COMPARISON OF SOME PHYSICAL CONSTANTS OF BENZENE WITH THOSE OF THIOPHENE AND FURAN

	Benzene	Thiophene	Furan
$k_{70°} \times 10^{4a}$	57	102.3	41.3
E^b	11,400	11,670	11,550
α^c	110,000	292,700	98,700
$\mu \times 10^{18d}$	0	0.63	0.71
$\eta \times 10^{4e}$	64.4	66.3	39.7
Parachor	192.1	187.4	
$M_D{}^f$	26.1	24.3	18 28
a^{1g}	5.8	5.6	5 4
b^g	5.9	5.7	5.55

[a] Catalytic action as a solvent on velocity of reaction between ethyl iodide and trimethylamine.

[b] Average value between 50 and 70° of E in the equation $K = \alpha e^{-E}/RT$ for the same reaction.

[c] Average value of α in same reaction.

[d] Dipole moment.

[e] Viscosity (internal pressure).

[f] Molecular refraction.

[g] Size and form of the liquid molecule measured by Roentgen rings.

Chemical Properties.—*Replacement reactions*, on the basis of which superaromatic properties[2] are claimed, occur more readily than with benzene, less so than with furan. The active position is alpha, although not so exclusively as in the case of furan. Bromination in cold acetic acid or benzene yields chiefly 2,5-dibromothiophene[15] with some monobromo product. In the absence of a solvent and with additional bromine, tri- and tetra-substituted derivatives[16] result. Meyer's method for obtaining the monobromo product (30 per cent yield) was to add gradually and with shaking the equivalent quantity of bromine. Better control of the process[16] results by use of (*a*) bromoacetamide at −5° in acetone (52 per cent yield), (*b*) cyanogen bromide with a trace of bromine in carbon disulfide or benzene (60 per cent yield), or (*c*) bromine at −10° in acetic acid (56 per cent yield). So pronounced is the tendency toward nuclear substitution that bromination of thiotolene, the sulfur analogue of toluene, yields bromothiotolene,[16b] $Br{\cdot}C_4H_2S{\cdot}CH_3$, under conditions that would lead to side-chain substitution of toluene.

Chlorination also reveals the greater reactivity of the hydrogen atoms in the heterocyclic system. Hypochlorous acid, for example, readily chlorinates thiophene[17] even when dissolved in benzene. Part of the sulfur is oxidized to sulfate in the process. Acetochloroamide, but not cyanogen chloride,[16] forms the monochloro[16] compound. The compound analogous to benzyl chloride must be obtained by indirect methods such as by treating thionyl alcohol with hydrochloric acid because the ring is chlorinated so easily.

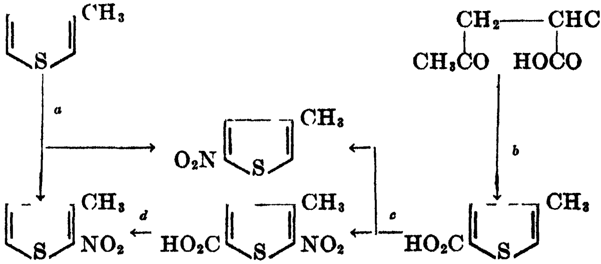
---

[15] TÖHL and SCHULTZ, *Ber.*, **27**, 2834 (1894).

[16] (*a*) STEINKOPF and OTTO, *Ann.*, **424**, 61 (1921); (*b*) STEINKOPF, AUGESTAD-JENSEN, and DONAT, *ibid.*, **430**, 78 (1923); STEINKOPF and KÖHLER, *ibid.*, **522**, 17 (1936); (*c*) KRAUSE and RENWANZ, *Ber.*, **62**, 1710 (1929). See Ref. 15 also.

Direct iodination[10] of thiophene occurs in the presence of a mild oxidizing agent such as mercuric oxide at room temperature, whereas more severe conditions (nitric acid and a higher temperature) are necessary for benzene. Here, too, nuclear is preferred to side chain substitution; thiotolene, refluxed in an acetic acid solution with iodine and mercuric acetate, forms 3,4,5-triiodo-2-methylthiophene.[18]

Nitration under such mild conditions as in acetic acid at −10° is sufficient for thiophene. A nitro group can replace not only a hydrogen atom, but a carboxyl group as well during nitrations. In this respect, thiophene is between benzene and furan.[19] For example, nitration of *o*-toluic acid gives substitution only; nitration of the analogously constituted 3-methylthiophene-2-carboxylic acid gives substitution and some replacement of carboxyl; nitration of the corresponding furan compound gives replacement only.



ᵃ HNO_3 in Ac_2O at −10°. Nitration chiefly in the 2-position. ᵇ (1) α-Methyllevulinic acid, derived from ethyl acetoacetate and α-bromopropionate, treated with P_2S_5; (2) partial oxidation of 2,4-dimethylthiophene by $KMnO_4$ at room temperature. ᶜ HNO_3. ᵈ Decarboxylation.

FIG. 1.—Proof of position of entering nitro group.

Failure of the hetero sulfur atom to be so exclusively ortho directing, as is the oxygen atom in furan, is illustrated by 2-nitro-3-methylthiophene and its furan analogue. The former on further nitration yields chiefly a β- while the latter yields exclusively an α-substituted product. Methods used by Rinkes[19] to prove the structure of these thiophene compounds are shown in Figs. 1 and 2.

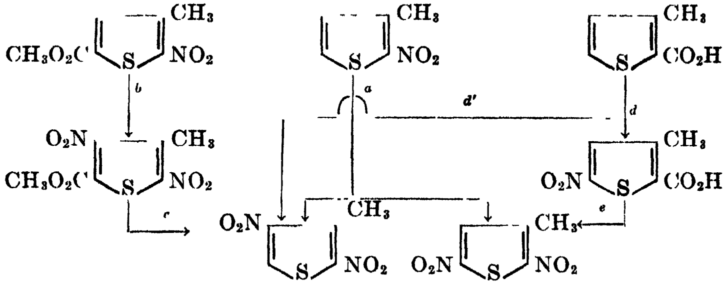
Acetylation and benzoylation occur readily under the influence of aluminum chloride in carbon disulfide.[20] The thiophene must be added with the acid chloride to avoid formation of tars. Phosphoric anhydride or stannic chloride may also be used as a catalyst.[21] Thienyl phenyl ketone[22] can be prepared indirectly by the action of benzoyl chloride on the mercurated thiophene, thienylmercuric chloride. These ketones are valuable because they can be reduced by the Clemenson method or, better, by the Wulff-Kizhner reaction to alkanes or benzyl derivatives.

---

[17] ARDAGH and BOWMAN, *J. Soc. Chem. Ind.*, **54**, 267 (1935).

[18] STEINKOPF and HANSKE, *Ann.*, **527**, 264 (1936); **541**, 238 (1939); STEINKOPF, SCHMITT, and FIEDLER, *ibid.*, **527**, 237 (1936).

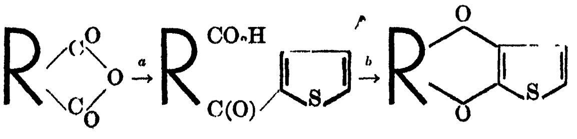
[19] RINKES, *Rec. trav. chim.*, **52**, 1052 (1933).



[a] HNO_3 in Ac_2O at −10°. The chief product is the 2,4-dinitro compound. [b] Methyl 3-methyl-2-nitrothiophene-5-carboxylate, obtained as shown in Fig. 1, is treated with HNO_3 in Ac_2O at −10°. [c] Saponification followed by decarboxylation in boiling quinoline over Cu. [d] Nitration in acetic anhydride at −10° of 3-methylthiophene-2-carboxylic acid which is prepared from 3-methylthiophene by successive treatment with mercuric oxide, iodine, magnesium and carbon dioxide. The chief product of this nitration is 4-nitro-3-methylthiophene-2-carboxylic acid. [d′] Nitration of the chief product with HNO_3 + conc. H_2SO_4 causes replacement of the carboxyl group by nitro. [e] HNO_3 + conc. H_2SO_4.

FIG. 2.—Interrelation of products that proves the position of nitration.

When benzoylation is carried out with phthalic anhydride, the resulting product loses water at 150° with phosphorus pentoxide and forms thiophanthrenequinone.[23] If the alpha positions are blocked by methyl groups, as in 2,5-dimethylthiophene, the β,β'-product results. These reactions parallel the formation of anthraquinone.



[a] C_4H_4S + $AlCl_3$. [b] P_2O_5 at 150° or H_2SO_4 at 105°.

Chlorosulfonic acid, which is a general reagent for the introduction of sulfonic acid groups into molecules with readily replaceable hydrogen atoms, gives a good yield of the mono product. Fuming sulfuric acid introduces a second substituent. The meta-directive influence of a sulfonic acid offsets somewhat the tendency for alpha substitution. For example, nitration of the monosulfonyl chloride (from the sodium sulfonate and phosphorus pentachloride) with fuming nitric acid produces mostly 4- with some 5-nitrothiophenesulfonic acid, as shown by hydrolysis of the mixture with aqueous sulfuric acid at 130 to 145° to give 3-nitrothiophene and hydrolysis of the residue at 150 to 160° to give 2-nitrothiophene.[24]

---

[20] COMEY, *Ber.*, **17**, 790 (1884); MINNIS, *Org. Syntheses*, **12**, 62 (1932); Coll. vol. II, 520.

[21] STEINKOPF, *Ann.*, **413**, 349 (1917); STADNIKOFF and RODOWSKY, *Ber.*, **61**, 269 (1928).

[22] VOLHARD, *Ann.*, **267**, 179 (1892).

[23] STEINKOPF, *ibid.*, **407**, 94 (1915); STEINKOPF, BARLAG, and V. PETERSDORFF, *ibid.*, **540**, 7 (1939).

Ethylsodium readily introduces a sodium atom[25] at the 2-position. Even ethylmagnesium bromide, if allowed to react at 160 to 170° in dimethylaniline, will form thiophenemagnesium[26] bromide, which, by carbonation, yields thiophene-2-carboxylic acid. Mercuration forms crystalline products that are useful for characterization[10] and occurs sometimes even when both alpha positions are occupied. For example, 2,5-dimethyl- and 2,5-diphenyl-thiophene form mercuric derivatives, but 2,5-dichloro-, dibromo-, dipropyl-, diisoamyl-, ethylpropyl-, bromoethyl-thiophene yield no product of this type. Neither do 3,4-diphenyl- and 2-nitrothiophene undergo mercuration.[16]

Addition reactions are more limited than with furan systems. Sodium amalgam will reduce thiophene-2,5-dicarboxylic acid to a tetrahydro product.[27] Hydrogenated derivatives of thiophene compounds are, however, usually synthesized by other methods, as in the reaction of α,δ-diiodoalkanes[28] with potassium sulfide. Tetramethylene glycol and hydrogen sulfide over alumina at 400° also yield (62.5 per cent) tetrahydrothiophene[29] (sometimes called thiophane). Although catalytic hydrogenation of thiophene does not appear to be practical, dehydrogenation of the tetra product over platinum on charcoal or nickel sulfide on alumina yields thiophene, although with considerable decomposition.[30]

Maleic anhydride[31] forms no adduct with thiophene. Activity as a conjugate system can, however, be increased by substituents that put a strain on the thiophene nucleus. For example, 2,3,4,5-di(1,8-naphthylene)thiophene reacts satisfactorily either with maleic anhydride or with stilbene.[32] Tetraphenylthiophene, however, fails to react in this manner.

---

[24] Steinkopf and Höpner, *ibid.*, **501,** 174 (1933).

[25] Schorigin, *Ber.*, **43,** 1938 (1910).

[26] Challenger and Gibson, *J. Chem. Soc.*, 305 (1940).

[27] Ernst, *Ber.*, **19,** 3274 (1886).

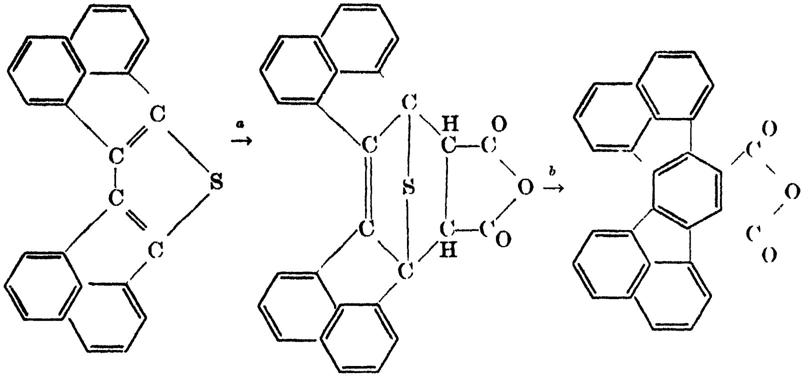
[28] v. Braun and Trümpler, *ibid.*, **43,** 545 (1910); v. Braun, *ibid.*, **43,** 3220 (1910).

[29] Jurjew and Medovshckikov, *J. Gen. Chem.* (*U.S.S.R.*), **9,** 628 (1939); *C.A.*, **33,** 7779 (1939).

[30] Jurjew and Borissow, *Ber.*, **69,** 1395 (1936).

[31] Delaby, *Bull. soc. chim.* [5], **4,** 765 (1937).

[32] Clapp, *J. Am. Chem. Soc.*, **61,** 2733 (1939).



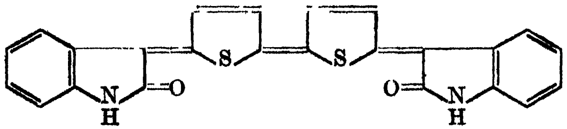
[a] Maleic anhydride at 225° for 15 min. [b] Elimination of H_2S by heat.

Ring opening is accomplished either by oxidizing or reducing agents. For example, cold concentrated nitric acid converts di- or tetra-bromothiophene to dibromomaleic acid, tribromo-β-thiotolene to bromocitraconic acid, and tribromo-α-thiotolene to dibromoacetylacrylic acid.[33] Piperidine[34] also eliminates sulfur from α-iodothiophene at 200°. The

$$\overline{C_4H_3S}-I + 2HNC_5H_{10} \rightarrow HI + H_2S + C_5H_{10}N-CH{=}C{=}C{=}CH-NC_5H_{10}$$

product is resinified by exposure to air but may be reduced by sodium and alcohol to tetramethylenedipiperidine. Reduction with hydriodic acid at 140° will remove sulfur.[35] Metallic sodium does not affect thiophene.

Tests for Thiophenes.—The reaction that led to the discovery of thiophene is still one of the common tests for its presence. Any thiophene that has hydrogen atoms in the 2,5- or 2,3-positions will form an indophenine; any compound that has the grouping $-\underset{O}{C}-\underset{O}{C}-$ (*e.g.* benzil, phenanthraquinone) can replace isatin as the coupling agent. The product has the structure



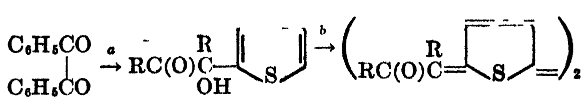
Formation of such products can be accomplished stepwise through an intermediate tertiary carbinol as illustrated with benzil below.

---

[33] ANGELI and CIAMICIAN, *Ber.*, **24**, 74, 1347 (1891).

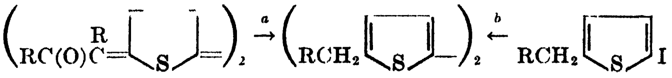
[34] TOHL, *ibid.*, **28**, 2217 (1895).

[35] KLAGES and LIECKE, *J. prakt. Chem.*, [2] **61**, 307 (1900).



[a] $C_4H_3S{\cdot}MgI$. [b] $H_2SO_4 + HOAc$. $R = C_6H_5$.

The presence of a bithienyl group is proved[18] by (*a*) reduction of the blue indophenine product with zinc and acetic acid and elimination of a benzoyl group from the leuco product to give 5,5′-dibenzyl-2,2′-bithienyl by sodium ethoxide, and (*b*) an independent synthesis of the bithienyl compound.



[a] Degradation by reduction with zinc and acetic acid followed by elimination of the benzoyl group by treatment with sodium ethoxide.

[b] Synthesis by treatment of the iodo compound with copper. The iodo compound is made by steps which commence by a condensation of benzyl alcohol with thiophene under the influence of zinc chloride, followed by mercuration of the α-benzylthiophene with mercuric chloride, and then by replacement of mercury by iodine under the agency of iodine and potassium iodide.

Liebermann's[36] test—the violet-formed blue color addition of a few drops of nitrous-containing sulfuric acid to a suspected benzene solution—is not given by all thiophene compounds. Thiotoluene produces a blue color, propyl- and butyl-thiophene give a blue-green color, and monochlorothiophene forms a blue color.

The presence of sulfur may, of course, be demonstrated in other ways. By passage over a platinum catalyst under dehydrogenation conditions, the sulfur is converted to hydrogen sulfide. The latter with dimethyl-*p*-phenylenediamine yields methylene blue (see Chap. XV). A sensitivity of 10^{-6} to 10^{-5} per cent thiophene is claimed.[37]

Special Compounds.—α-Thiophenaldehyde[38] (b.p. 198°) results from distillation of thienylglyoxylic acid, a compound derived by oxidation of acetothienone. It undergoes all the reactions, such as the Cannizzaro and Perkin synthesis, that are exhibited by benzaldehyde or furfural. 3,4-Dibromothiophene-2,5-dialdehyde (the corresponding dichloro compound likewise) is made by bromination of the 2,5-dimethylthiophene (sometimes called 2,5-thioxen) and hydrolysis of the 3,4-dibromo-2,5-di(dibromomethyl)thiophene[39] product. Potassium permanganate converts the dialdehyde readily to the dibromodiacid derivative. Strong potassium hydroxide induces a Cannizaro reaction. The dialdehyde, with aniline, forms a dianil, $C_{18}H_{12}Br_2N_2S$, the color of which is more intense than that of the corresponding compound in the aromatic series, probably because the double bonds in the thiophene ring can undergo conjugation readily with bonds outside the ring. Condensation of the dialdehydes with diamines, such as hydrazine or *o*-phenylene diamine, yields products that may exist in macrocyclic rings.[40] 2-Ethyl-5-methyl-thiophene (b.p. 159.8 to 160.4°) is prepared[41] by the action of moist powdered potassium hydroxide on the semicarbazone of 2-methyl-5-acetothiophene—a modified Wolff reduction. Unlike most thiophene compounds, it has a characteristically pleasant odor somewhat like that of *p*-ethyltoluene.

---

[36] LIEBERMANN, *Ber.*, **16**, 1473 (1883); **20**, 3231 (1887).

[37] GILLO, *Ann. chim.*, **12**, 281 (1939); *C.A.*, **34**, 1531 (1940).

[38] HANTZSCH, *Ber.*, **24**, 47 (1891); GOLDSCHMIDT and ZANOLI, *ibid.*, **25**, 2588 (1892).

[39] STEINKOPF and KÖHLER, *Ann.*, **532**, 250 (1937).

2,3-Dichlorothiophene[39] is obtained by a very unusual reaction. Hydrogen chloride is passed through a hot saturated acetic acid solution of 2,3-dibromothiophene-5-carboxylic acid. The two bromine atoms are replaced by chlorine. Carbon dioxide is then driven out of the molecule by a hot acetic acid solution of mercuric acetate and the resulting dimercuri product is then heated with dilute acid. The dichloro product boils at 173 to 174°. Other chloro compounds of thiophene are made by the more common method of direct substitution.

3-Nitrothiophene (m.p. 75 to 77°, b.p. 225° corr.) forms no mercuric chloride nor indophenine compound. Reduction with tin and hydrochloric acid gives 3-thiophenin, which is easily resinified as the free base, but can be isolated as the hydrochloride of the stannic chloride double salt $(C_4H_6NClS)_2SnCl_2$ or as the benzoyl or acetyl derivative (m.p. 153.5 and 145.8, respectively).[24]

Thiophenin,[42] the 2-amino derivative corresponding to aniline, is made by reduction of the corresponding nitro compound with tin and alcoholic hydrochloric acid. It is isolated as a double salt with stannic chloride. The amine forms azo dyestuffs readily with diazonium salts, but forms only tars and a little nitrothienol, $NO_2 \cdot C_4H_2S \cdot OH$, with nitrous acid.

α,α'-Dithienyl (m.p. 33°) results from pyrolysis[43] of thiophene in a red-hot tube. Some of the β,β'-isomer (m.p. 132°) forms simultaneously. The α,α'-product forms also during sulfonation[44] of thiophene with cold weakly fuming sulfuric acid. Treatment of α-thiophenemagnesium bromide with cupric chloride[45] gives the same product in 44 per cent yield. This last method is general for coupling with the Grignard reagent,[46] the yields with ferrous chloride, cobaltous bromide, and nickel bromide being nearly quantitative in the case of phenylmagnesium bromide.

---

[40] Steinkopf and Eger, *Ann.*, **533**, 270 (1937); Steinkopf, Leitsmann, Müller, and Wilhelm, *ibid.*, **541**, 260 (1939).

[41] Shepard, *J. Am. Chem. Soc.*, **54**, 2951 (1932).

[42] Stadler, *Ber.*, **18**, 2316 (1885).

[43] Nahnsen, *ibid.*, **17**, 789, 2197 (1884); v. Auwers and Bredt, *ibid.*, **27**, 1746 (1894).

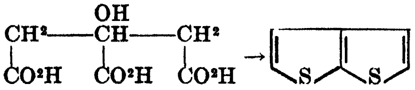
[44] Thöl, *ibid.*, **27**, 665 (1894).

[45] Steinkopf and Roch, *Ann.*, **482**, 251 (1930).

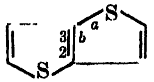
[46] Gilman and Lichtenwalter, *J. Am. Chem. Soc.*, **61**, 957 (1939).

Tetraphenylthiophene (Thionessal) (m.p. 184°), results from pyrolysis of thiobenzaldehyde or from fusion of stilbene with sulfur.[47]

Thiophthene (b.p. 225°) results when citric acid is heated with phosphorus trisulfide.[48]



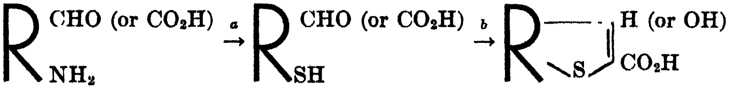
Thieno [3,2-*b*] thiophene (m.p. 54°) is the isomer of thiophthene. It is one of the higher boiling compounds that results from passing acetylene over boiling sulfur.[26] Its structure is shown by X-ray analysis and a



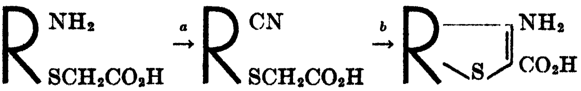
zero electric moment.

CONDENSED THIOPHENE SYSTEMS

Thionaphthene Compounds.—Preparation of fused benzene-thiophene systems is similar to many of the processes used in the synthesis of coumarones. Common starting points are *o*-substituted thiophenols which are readily derived from appropriate amino compounds by way of the diazonium salt or from halogen compounds by treatment with sodium sulfide. Ring closure by dehydration of a thiophenoxy derivative, X—C_6H_4S—CH_2COOH, completes the synthesis. Typical preparations are illustrated in Fig. 3.



[a] HNO_2, KSCN + CuSCN, Na_2S. [b] $ClCH_2CO_2Na$ followed by dehydration with H_2SO_4 or P_2O_5.



[a] HNO_2, $CuSO_4$ + KCN. [b] Heat with aqueous NaOH, neutralize with ice and HCl.

FIG. 3.—Methods[49] for synthesis of thionaphthene compounds by forming the 2,3-bond.

Thionaphthene (m.p. 32°) can be isolated from shale oil[50] and is apt to be found in coal tar, associated with naphthalene, in the way that thiophene is associated with benzene. Its separation from naphthalene by sulfuric acid at 90° is accompanied by considerable resinification, because this sulfur compound is similar to coumarone and indene which are easily polymerized. A better method[51] is to precipitate the mercuric acetate derivative and then recover the thionaphthene with hydrochloric acid. Hydrogen peroxide in aqueous acetic acid forms also thionaphthene dioxide.[52]

---

[47] BAUMANN and KLETT, *Ber.*, **24**, 3310 (1891).

[48] BIEDERMANN and JACOBSEN, *ibid.*, **19**, 2444 (1886).

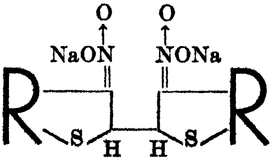
[49] (*a*) FRIEDLÄNDER, *Ann.*, **351**, 390 (1907); (*b*) FRIEDLÄNDER and LENK, *Ber.*, **45**, 2083 (1912); (*c*) FRIEDLÄNDER and LASKE, *Ann.*, **351**, 412 (1907).

[50] CHALLENGER and MILLER, *J. Chem. Soc.*, 1005 (1939).

Chemically, this heterocyclic compound resembles naphthalene more than its analogue in the benzofuran series. Substitution usually occurs in the 3-position, corresponding to the alpha-position in naphthalene. Hot alcoholic mercuric chloride or aqueous acetic mercuric oxide forms di derivatives, $C_8H_4S(HgX)_2$; cold aqueous mercuric acetate forms a mono derivative, $C_8H_4S(HgO_2CCH_3)$. Treatment of the mono compound with propionyl chloride gives 3-thionaphthenyl ethyl ketone, the same compound that is formed from thionaphthene, propionyl chloride, and stannic chloride in carbon disulfide. Oxidation of the ketone with potassium ferricyanide yields thionaphthenyl-3-carboxylic acid (m.p. 174 to 175°) which is different from the 2-isomer (m.p. 114°) obtained synthetically as in Fig. 3. These steps constitute proof of the position of the substituent.

Bromination[53] also affects the 3-position. β-Bromothionaphthene forms a Grignard reagent with difficulty; but in the presence of over 2 moles of a readily reactive halide, with magnesium equivalent to the total halide, a yield of 70 per cent of thionaphthene-3-carboxylic acid[54] is obtained by carbonation of the mixture of Grignard reagents. This procedure is that used by Grignard for unreactive halides.

Fuming nitric acid inserts a nitro group in the 3-position.[55] Reduction with stannous chloride and hydrochloric acid converts this product to the 3-amino compound identical with the synthetic product obtained by Friedländer by decarboxylation of a compound shown in Fig. 3. When the amine is heated with acid, 3-hydroxythiophene is produced. Reduction of the nitro compound with sodium sulfide in boiling alcohol gives the sodium salt of aci-dinitro-3,3′-(dithionaphthenyl-2,2′-tetrahydride-2,3,2′,3′) shown below. The process is very similar to pinacol formation, such as occurs by a 1,4-process in reduction of benzalacetone.



---

[51] Weissgerber and Kruber, *Ber.*, **53**, 1551 (1920).

[52] Lanfry, *Compt. rend.*, **154**, 519 (1912).

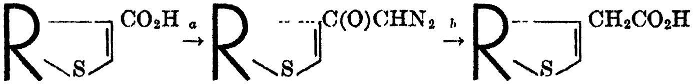
[53] Komppa, *J. prakt. Chem.*, **122**, 319 (1929).

[54] Crook and Davies, *J. Chem. Soc.*, 1697 (1937).

[55] Fries and Hemmecke, *Ann.*, **470**, 1 (1929).

In contrast to other agents, organoalkali metal compounds place a metal in the 2-position. Ethylmagnesium bromide in hot dimethylaniline forms thionaphthenylmagnesium bromide which on carbonation changes to the 2-carboxylic acid. Sodamide in xylene at 100 to 145° forms mono- and di-sodium compounds which on carbonation produce thionaphthene-2-carboxylic acid and the 2,3-dicarboxylic acid. This last compound readily forms an anhydride, which, with saturated ammoniacal methyl alcohol, yields both the 2- and the 3-amide derivatives. The former has the higher melting point (221°) and, therefore, separates first in 50 to 70 per cent yield; the latter melts at 193° and separates from the concentrated mother liquor.

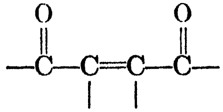
Thionaphthene-3-acetic acid (m.p. 109°) has less growth-promoting activity than the structurally related heteroauxin, the plant hormone. The synthesis used for the compound in the indole series is not applicable to this thio analogue, which is prepared[54] from the 3-carboxylic acid by the Arndt-Eistert reaction shown below.



The starting material is prepared from 3-bromothionaphthalene, magnesium, and methyl iodide followed by carbonation.

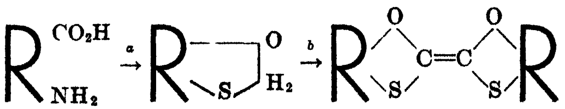
[a] $SOCl_2$ followed by CH_2N_2. [b] Ag_2O + alcohol followed by hydrolysis of the ester.

Thioindigo Dyes.—Dyes of this series contain the grouping



$$-\overset{O}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-\overset{O}{\overset{\|}{C}}-$$

characteristic of indigoid dyes. The number is very large, because substituents in these compounds have a much greater effect on color than they do in indigo. Friedländer[56] discovered the first member (called thioindigo red) of this group by use of a series of reactions patterned as much as possible after Heumann's synthesis of indigo. Other methods



[a] Same steps as shown in Fig. 3 for preparation of the 3-hydroxy-2-carboxylic acid compound, followed by decarboxylation and proton shift. [b] K_3FeCN_6.

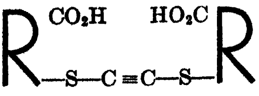
of preparation are (*a*) by action of chlorosulfonic acid on acetylene bis-thiosalicyclic acid[57] and (*b*) by aerial oxidation of o-thiolacetophenone[58] under alkaline influence.

---

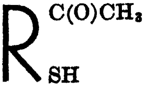
[56] Friedländer, *Ber.*, **39**, 1060 (1906).

[57] German patent 205,324, *Chem. Cent.*, I, 605 (1909).

[58] German patent 198,509, *ibid.*, I, 2118 (1908).

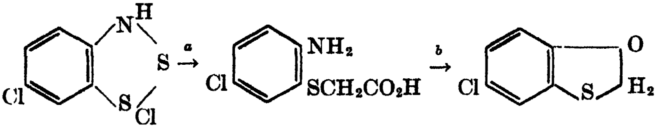


(a)

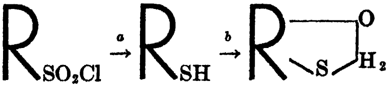


(b)

Aniline and sulfur chloride[59] give an intermediate that can be converted to a chloro-substituted thioindigo. Benzenesulfonyl chloride can be reduced to a thiophenol which can also be converted to a dye-forming intermediate by the usual set of reactions.

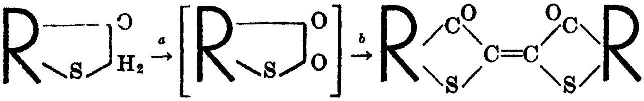


[a] The addition product of the reaction of aniline and sulfur chloride is hydrolyzed and the thiophenol made to react with chloroacetic acid. [b] HNO_2, CuCN, H_2O, ring closure, and decarboxylation.



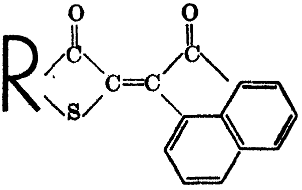
[a] Zn + Aq·H_2SO_4. [b] NaOH + $ClCH_2CO_2H$, $ClSO_3H$ or H_2SO_4 to close ring.

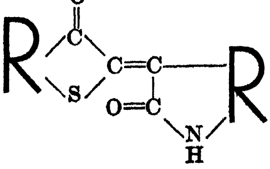
Formation of these dyestuffs may proceed by way of oxidation of one molecule of thioindoxyl to a diketo compound which then condenses with unchanged thioindoxyl.



[a] Oxidation. [b] Reaction with thioindoxyl.

Any other diketo compound will similarly condense with the active methylene group in thioindoxyl. Examples are the formations of ciba scarlet G[60] and thioindigo scarlet R[61] by condensation with acenaphthenequinone and isatin, respectively, under the influence of hydrochloric–acetic acid.





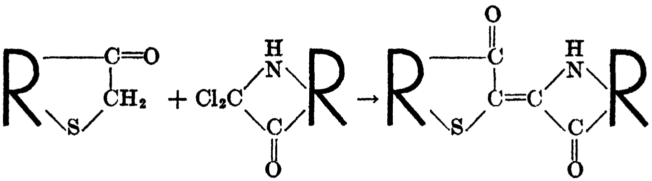
---

[59] Herz, German patent 360,690; U.S. patent 1,243,170, *C.A.*, **12**, 227 (1918); Hixon and Cauwenberg, *J. Am. Chem. Soc.*, **52**, 2118, 2125 (1930).

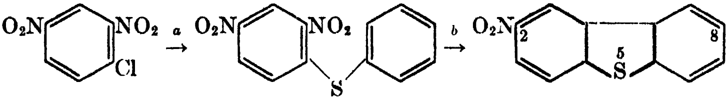
[60] Grob, *Ber.*, **41**, 3331 (1908).

[61] Bezdzik and Friedländer, *Monatsh.*, **29**, 375 (1908); Felix and Friedländer, *ibid.*, **31**, 55 (1910).

Dyes that have a link to the 2-position of the isatin nucleus can be made by first preparing isatin chloride from phosphorus pentachloride and isatin and than condensing with thioindoxyl.

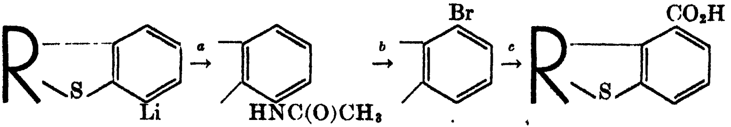


Dibenzothiophene.—This compound (m.p. 99°, b.p. 333°) is conveniently prepared (65 to 70 per cent yield) by the action of aluminum chloride on a fused mixture of biphenyl and sulfur.[63] The synthesis of substituted dibenzothiophenes parallels the methods used for diphenylene oxide.[62]



[a] $NaSC_6H_5$. [b] $SnCl_2 + HCl$, HNO_2, $H_2SO_4 + H_2O$.

Nitrating, sulfonating, acylating, and halogenating agents attack the 2-position; butyllithium[63] introduces a lithium atom in the 4-position; and phenylcalcium iodide[64] forms the 3-dibenzothiophenecalcium iodide. Introduction of substituents into the 1-position is accomplished by indirect methods[63] such as are illustrated with partial formulas below. Addition of sodium in liquid ammonia yields 1,4-dihydrodibenzothiophene. All these reactions are reminiscent of those with dibenzofuran, save for nitration, which in the oxygen analogue enters both the 2- and 3-position, but predominately the latter, and save for the introduction of calcium at the 3-position of the thio compound. In addition, the thio analogue undergoes ready oxidation with potassium dichromate to the 5-dioxide. Fusion of this sulfone with sulfur restores the dibenzothiophene.[65]



[a] Br_2, $NH_3 + CuBr$ at 210-220°, $(CH_3CO)_2O$. [b] Br_2, $HX + H_2O$, HNO_2, H_2SO_4. [c] Mg, CO_2.

---

[62] Cullinane, Davies, and Davies, *J. Chem. Soc.*, 1435 (1936).

[63] Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

[64] Gilman, Jacoby, and Pacevitz, *ibid.*, **3**, 120 (1938).

[65] Cullinane and Davies, *Rec. trav. chim.*, **55**, 881 (1936).

Problems

1. Write equations for the preparation of the following heterocyclic compounds from readily obtainable nonheterocyclic reagents: (*a*) 2-Methyl-4-ethyl thiophene.[41] (*b*) 2,3-Dimethylthiophene.[41] (*c*) 3-Iodo-2,5-dimethylthiophene.[66]

2. How would you prepare the following compounds from thiophene?[39] (*a*) 2-Chlorothiophene. (*b*) 2-Chloro-5-iodothiophene. (*c*) 2,3-Dichlorothiophene. (*d*) 3-Chlorothiophene. (*e*) 3-Chlorothiophene-2-carboxylic acid.

3. What is the product when the following compounds are allowed to react together under the conditions described? (*a*) 3-Methyl-1,3-pentadiene and sulfur at 350°.[10] (*b*) Mucic acid and barium sulfide heated with phosphorus trisulfide.[8] (*c*) Thiophenol distilled with litharge.[67] (*d*) Styrene or stilbene heated with sulfur.[68] (*e*) Acenaphthene fused with sulfur.[68] (*f*) Methyl acetylenedicarboxylate heated with sulfur at 150 to 155° in a sealed tube.[68]

4. Give a suitable sequence of reactions for the preparation of 2-ethyl-5-methylthiophene from 2-methylthiophene.[41]

5. What is the product of the following reaction? (*a*) 2-Iodothienyl-5-mercuric chloride with arsenic trichloride.[69] (*b*) Nitric acid on bromothiophene in acetic anhydride at 0°.[70] (*c*) α-Thiophenesulfonic acid distilled with potassium cyanide.[71] (*d*) Thiophene stirred with succinic anhydride and aluminum chloride at 0° in nitrobenzene.[72] (*e*) 2,5-Dimethylthiophene with succinic anhydride and aluminum chloride in nitrobenzene.[66] (*f*) Thiophene with 2,5-dichloro-2,5-dimethylhexane in the presence of stannic chloride.[73] (*g*) Dinaphthylenethiophene heated with stilbene.[32] (*h*) A mixture of thiophene and iodine treated drop by drop with dilute (50 per cent) nitric acid.[74]

6. What product is produced from *p*-methoxyacetophenone by the following sequence of reagents?[75] (*a*) Furfural and sodium methoxide at 0°, followed by gradual warming to room temperature. (*b*) Hot alcoholic hydrochloric acid. (*c*) Ethereal solution of diazomethane. (*d*) Phosphorus pentasulfide at 90 to 100° until no more hydrogen sulfide is evolved. (*e*) Hydrazine hydrate solution at reflux temperature. (*f*) Nitrous acid (sodium nitrite and hydrochloric acid) in the cold. (*g*) Methyl-alcoholic barium hydroxide at reflux temperature, followed by crystallization of the hydrochloride of the product, which has the composition $C_{16}H_{15}ONS \cdot HCl$.

7. Selenium has many properties that are similar to those of sulfur. Devise methods for synthesis of the following selenophens, the selenium analogues of thiophenes: (*a*) α,α′-Dimethylselenophen (sometimes called selenoxen).[76] (*b*) Selenophene and selenophthene.[77]

8. Devise a sequence of reactions for the preparation of 5-hydroxythionaphthene[72] from *o*-chlorobenzaldehyde.

---

[66] Steinkopf, Poulsson, and Herdey, *Ann.*, **536**, 128 (1938).

[67] Cullinane and Padfield, *J. Chem. Soc.*, 1131 (1935).

[68] Baumann and Fromm, *Ber.*, **30**, 110 (1897); Michael, *ibid.*, **28**, 1633 (1895).

[69] Finzi, *Gazz. chim. ital.*, **62**, 244 (1932); *C.A.*, **26**, 4329 (1932).

[70] Babasinian, *J. Am. Chem. Soc.*, **57**, 1763 (1935).

[71] Douglas, *Ber.*, **25**, 1311 (1892); Meyer and Kreis, *ibid.*, **16**, 2172 (1883).

[72] Fieser and Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

[73] Bruson and Kroeger, *ibid.*, **62**, 36 (1940).

[74] Datta and Chatterjee, *ibid.*, **39**, 435 (1917).

[75] Robinson and Todd, *J. Chem. Soc.*, 1743 (1939).

[76] Paal, *Ber.*, **18**, 2255 (1885).

[77] Umezawa, *Bull. Chem. Soc. Japan*, **14**, 363 (1939); *C.A.*, **34**, 1309 (1940).

9. Write the reaction and name the product for each step in the following series of reactions: (*a*) Ethyl β-carbethoxylevulate, $CH_3C(O)CH(CO_2Et)CH_2CO_2Et$, is dissolved in alcohol, which has been saturated with dry hydrogen chloride at 0°, and is treated for 12 hr. with a stream of hydrogen sulfide. (*b*) The product from (*a*) is refluxed 4 to 6 hr. with barium hydroxide solution and the solution is then acidified with hydrochloric acid. (*c*) The product from (*b*) is dissolved in a minimum quantity of alcohol saturated with dry hydrogen chloride at 0° and is treated with an alcoholic solution of benzaldehyde to give a compound with the empirical composition $C_{23}H_{24}O_6S_2$. (*d*) The product from (*b*) is treated with hydrobromic acid at 0° and the mixture is then allowed to warm to room temperature for 1 hr. (*e*) The product from (*d*) is dissolved in an alcoholic solution of *o*-nitrobenzaldehyde, and is treated with a few drops of alcoholic hydrogen chloride. This product gives no coloration with ferric chloride and has the empirical composition $C_{13}H_9O_5NS$.[78]

10. Write the reactions and name the products obtained for each step in the following sequence[18] of reactions, which starts with ethyl phenylglyoxalate: (*a*) Thienylmagnesium iodide. (*b*) Concentrated sulfuric acid. (*c*) Zinc in boiling acetic acid. (*d*) Alkaline hydrolysis followed by acidification. (*e*) Heating with copper and quinoline to give $C_{22}H_{18}S_2$.

11. How would you prepare a thioindigo dye from *p*-cymene?[59]

12. 3-Hydroxythionaphthene should be able to exist in both an enol and a keto form. What reagents would be used to test this question?[79]

13. What is the product of the reaction of dibenzothiophene with succinic anhydride and aluminum chloride suspended in a mixture of tetrachloroethane and nitrobenzene?[63]

14. Devise a method for the synthesis of 5-hydroxy-2-methylthiophene from nonheterocyclic compounds.[80] On treatment of this product with ferric chloride in alcohol, dark-colored crystals result which are brownish black with a greenish luster after recrystallization from benzene. The molecular weight and analysis show the formula to be $C_{10}H_8O_2S_2$. What is the probable structure of the compound? Would the original thiophene compound react with acenaphthenequinone under the influence of hydrochloric acid?

15. *o*-Thiolbenzoic acid, added to a cold mixture of chlorosulfonic acid and malonic acid, yields a colored compound, $C_{16}H_8O_2S_2$. What is the probable structure of the compound and what are the steps in its formation? What would be the product of the reaction of *o*-thiolbenzoic acid with ethyl acetoacetate under these conditions?[81]

---

[78] MITRA, CHAKRABARTY, and MITRA, *J. Chem. Soc.*, 1116 (1939).

[79] v. AUWERS and THIES, *Ber.*, **53**, 2285 (1920).

[80] STEINKOPF and THORMANN, *Ann.*, **540**, 1 (1939).

[81] HUTCHINSON and SMILES, *J. Chem. Soc.*, **101**, 570 (1912).

CHAPTER IV

PYRROLES

Pyrroles are widely distributed in nature, chiefly in porphyrins and like compounds. The parent member, pyrrole, was detected in 1834 by Runge,[1] who noticed that a pine splinter moistened with hydrochloric acid became a fiery red when exposed to vapors from the distillation of coal tar, bones, and horn. Hence the name pyrrole, from the Greek word for fiery red. It was not until 1858 that the compound was obtained pure and analyzed.[2] Shortly afterward, its synthesis was accomplished[3] by the dry distillation of ammonium mucate. Except for the addition of glycerol to prevent caking and to reduce loss of ammonia, this method is used today.[4]

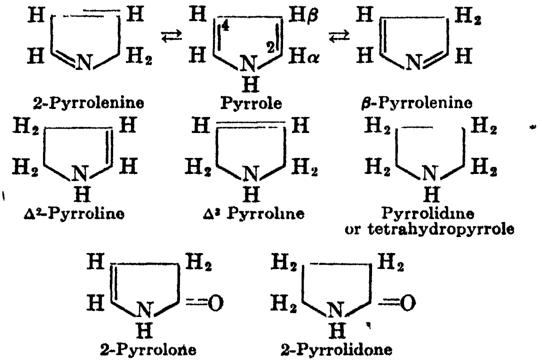
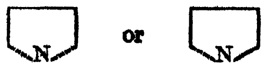


FIG. 1.—Naming, numbering, and formulas of pyrrole compounds.

Methods for Synthesis.—The wide variety of preparative methods may be classified into five large groups, depending on the sections to be joined. In the approximate order of importance, these methods are shown below with dotted lines to indicate bonds that must be formed:

(a) 

Appropriate 1,4-disubstituted compounds such as diketones, keto acids, diamines, amino-halogen compounds.

---

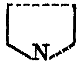
[1] RUNGE, *Ann. Physik* [2], **31**, 67, 74 (1834).

[2] ANDERSON, *Ann.*, **105**, 349 (1858).

[3] SCHWANERT, *ibid.*, **116**, 270, 278 (1860).

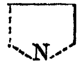
[4] GOLDSCHMIDT, *Z. Chem.*, **3**, 280 (1867); MCELVAIN and BOLLIGER, *Org. Syntheses*, Coll. Vol. **I**, 463 (1932).

(*b*)



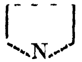
β-Keto esters or diketones with α-aminoketones.

(*c*)



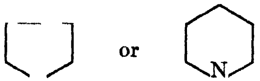
α-Keto esters, aldehydes, and amines.

(*d*)



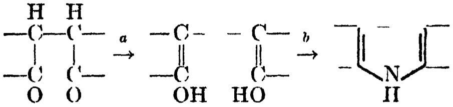
α-Chloroesters, α-keto esters, and amines.

(*e*)



Five or six-membered rings that can be converted to pyrroles.

From 1,4-Disubstituted Compounds.—The first of these methods includes the widely used Paal-Knorr synthesis, named from the independent discoveries of Paal[5] and Knorr.[6] The possible steps in this reaction are illustrated below by the conversion of γ-diketones to pyrroles when heated with ammonia. The process is capable of wide application. Succinaldehyde and ammonia give pyrrole;[7] acetonylacetone, $CH_3C(O)(CH_2)_2C(O)CH_3$ and ammonia (in the form of ammonium carbonate) at 115° give 2,5-dimethylpyrrole;[8] and succinyldiacetic ester, $EtO_2CCH_2C(O)CH_2CH_2C(O)CH_2CO_2Et$, warmed with an aqueous solution of methylamine, precipitates a quantitative yield of 1-methylpyrrole-2,5-diacetic ester.[9] The last named compound is especially important as a first step toward making ecgonin. Hydroxylamine,[6] glycine,[10] hydrazine,[11] and phenylhydrazine[12] may be used in place of ammonia and primary amines. Hydrazines sometimes cause the formation of pyridazines as well as pyrroles.



[a] Enolization. [b] Condensation with the amine.

Under the broad title of this section are included combinations that lead to pyrrolines, pyrrolones, pyrrolidines, and pyrrolidones (see Fig. 2).

From β-Keto Esters or Diketones and α-Aminoketones.—This second type of synthesis originated from Knorr's[13] work on the reduction of an isonitroso ketone by zinc and acetic acid in the presence of ethyl acetoacetate, as shown in the preparation of Knorr's pyrrole below. Conversion to an aminoketone occurs in the first stage. Indeed, it has been shown[14] that better yields are obtained if the aminoketone is prepared separately and then condensed with the β-diketone or keto ester. Acetic acid usually suffices to effect this condensation, but strong alkali may be used, particularly if the mixture is allowed to stand for several days or even months. Alkali, in fact, will cause[15] butanone-2 to condense with ethyl oxalacetate, whereas acetic acid will not.

---

[5] PAAL, *Ber.*, **18**, 367 (1885).

[6] KNORR, *ibid.*, **18**, 302, 1568 (1885); *Ann.*, **236**, 290 (1886).

[7] HARRIES, *Ber.*, **34**, 1488 (1901).

[8] YOUNG and ALLEN, *Org. Syntheses*, **16**, 25 (1936); Coll. vol. II, 219.

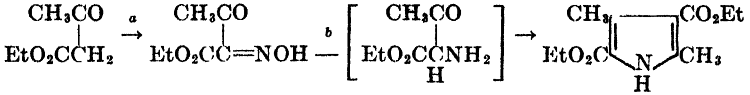
[9] WILLSTÄTTER and PFANNENSTIEL, *Ann.*, **422**, 14 (1921); D.R.P. 346,890.

[10] (*a*) KNORR, *Ann.*, **236**, 290 (1886); (*b*) PAAL and SCHNEIDER, *Ber.*, **19**, 3156 (1886).

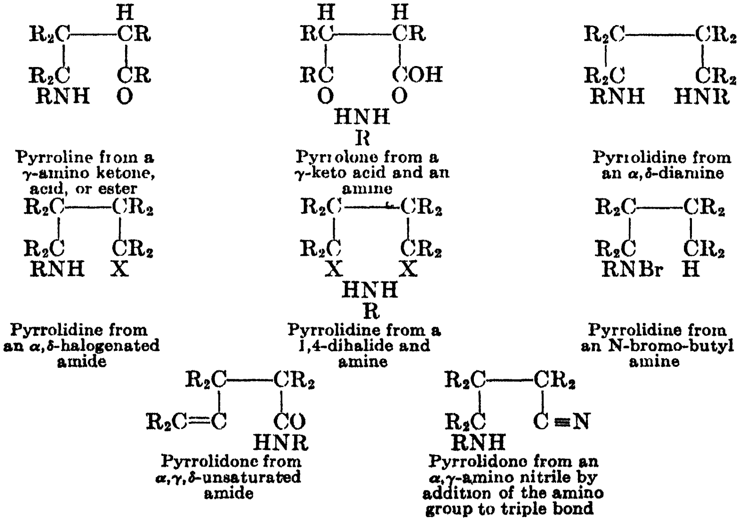
[11] KORSCHUN, *ibid.*, **37**, 2183, 2192 (1904).

[12] REISSERT and ENGEL, *ibid.*, **38**, 3281 (1905).

[13] KNORR, *ibid.*, **17**, 1635 (1884); *Ann.*, **236**, 317 (1886).



[a] HNO_2. [b] Zn + HOAc. The intermediate aminoketone condenses with a molecule of the ketoester.



Pyrroline from a γ-amino ketone, acid, or ester

Pyrrolone from a γ-keto acid and an amine

Pyrrolidine from an α,δ-diamine

Pyrrolidine from an α,δ-halogenated amide

Pyrrolidine from a 1,4-dihalide and amine

Pyrrolidine from an N-bromo-butyl amine

Pyrrolidone from α,γ,δ-unsaturated amide

Pyrrolidone from an α,γ-amino nitrile by addition of the amino group to triple bond

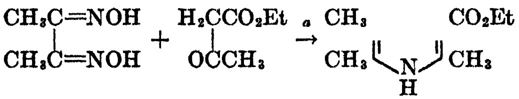
FIG. 2.—Structural diagrams that illustrate combinations for syntheses of reduced pyrrole systems from 1,4-disubstituted compounds. The hydrogen atoms eliminated are shown by H. R represents hydrogen, alkyl, aryl, or other common groups.

Isonitroso compounds are readily prepared by the action of nitrous acid on methylene groups activated by an adjacent carbonyl group. Acetone,[14] ethyl methyl ketone,[15] acetophenone,[14] ethyl acetoacetate,[14] acetylacetone,[14] acetone dicarboxylic ester,[14] and oxalacetic ester[15] readily form such products. Knorr's synthesis is capable, therefore, of extensive use. The use of a dioxime of a 1,2-diketone[16] with ethyl acetoacetate is in many ways an equivalent method.

[14] KNORR and LANGE, *Ber.*, **35**, 2998 (1902).

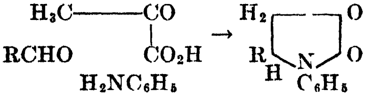
[15] (*a*) PILOTY and BLÖMER, *ibid.*, **45**, 3749 (1912); (*b*) PILOTY and HIRSCH, *Ann.*, **395**, 63 (1913).

[16] TREIBS, *ibid.*, **524**, 285 (1926).

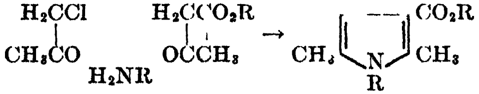


ᵃ Zn dust + HOAc.

From α-Ketopropionic Acids, Aldehydes, and Amines.—This synthesis is illustrated below with pyruvic acid. The yield of the diketopyrrolidine[17] is reduced by simultaneous formation of a dihydroquinoline (Döbner synthesis, page 264). Combinations that have been used effectively in this class have been composed of keto acids such as pyruvic acid, phenylpyruvic acid, and oxalacetic ester; aldehydes such as benzaldehyde, furfural, piperonal, cinnamaldehyde, and salicylaldehyde; and anilines such as aniline, toluidine, *p*-aminoacetophenone, *p*-aminobenzoic, and arsanilic acid.



From Chloroacetones, β-Keto Esters, and Amines.—This method, devised by Hantzsch,[18] produces not only a pyrrole but a furan compound as well. The substituents, however, are not in the same relative positions in the two types of products (compare with page 3). The pyrrole synthesis is probably preceded by the formation of an intermediate β-aminocrotonic acid, since β-keto esters and amines form such compounds readily.[19] The hydrogen for the hydrochloric acid eliminated in pyrrole formation then comes from the methylene group which is made active by the adjacent carboalkoxy group; but in furan formation, the hydrogen comes from the active hydrogen in the enol form of the keto ester.



From Ring Compounds.—Examples of this method of synthesis are shown in Fig. 3. Furans are converted to pyrroles by amines over aluminum oxide[20] at 450°; lactones are readily changed to lactams, and these in turn are reduced by sodium and amyl alcohol to pyrrolidines; and succinimides[21] are reduced to pyrroles by distillation over zinc dust or, better, by reduction with sodium and alcohol, catalytic (Pt) hydrogen, or electrolytic hydrogen.

---

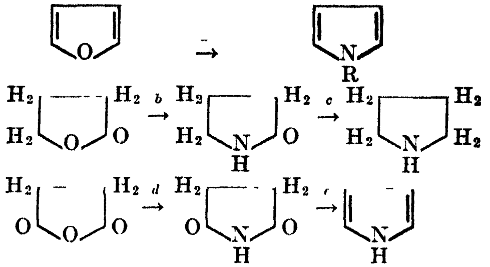
[17] Borsche, *Ber.*, **41**, 3884 (1908); **42**, 4072 (1909).

[18] Hantzsch, *ibid.*, **23**, 1474 (1890).

[19] Korschun, *ibid.*, **38**, 1125 (1905); Feist, *ibid.*, **35**, 1538 (1902).

[20] Jurjew and Rakitin, *ibid.*, **69**, 2492 (1936).

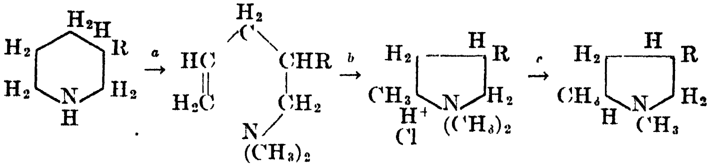
[21] Hollins, "Nitrogen Ring Compounds," p. 47, Ernest Benn, Ltd., London, 1924.



[a] $Al_2O_3 + RNH_2$ + heat. [b] NH_3. [c] Na + EtOH. [d] NH_3. [e] Zinc dust and heat.

FIG. 3.—Synthesis of pyrroles and pyrrolidines from oxygen-containing compounds.

Exhaustive methylation has been applied also as a step in the conversion of a piperidine to a pyrrolidine. The process (see Fig. 4) is equivalent to formation of a 1,4-disubstituted compound. This method[22] is applicable to 3- but not to 2-alkylated piperidines.



[a] Exhaustive methylation (see page 307). [b] Addition of HCl to double bond followed by intramolecular salt formation. [c] Distilled with concurrent loss of CH_3Cl.

FIG. 4.—Conversion of a piperidine to a pyrrolidine.

Reactions of Pyrroles.—Th[illegible]cal behavior of pyrroles is greatly influenced by the presence of an imino group, which sometimes acts as an imino phenol and at other times acts as if it were part of an imine-ketimine system, like the enol-keto system in ethyl acetoacetate, but with an additional vinyl group. In addition, some reactions typical of a butadiene or unsaturated system occur, and the presence of a functional group within the ring facilitates ring opening. As usual when so many reactive units are grouped under one roof, the properties that characterize each system are affected by neighboring types. The net result is a behavior that can be considered typical for pyrroles but with many evidences of the individual patterns that belong to the simpler systems.

Acidic and Phenol-like Properties.—Formation of metallic derivatives of pyrrole is obviously more difficult than in the case of phenol, since the acid dissociation constants are different, $10^{-16.5}$ and 10^{-10}, respectively. Metallic potassium in petroleum ether liberates hydrogen forming pyrrylpotassium. Sodium does not similarly attack pyrrole itself, but does form a sodium salt with 2,4-dimethyl-3,5-dicarbethoxypyrrole.[23]

---

[22] MERLING, ANN., **264**, 310 (1891); JACOBI and MERLING, *ibid.*, **278**, 8 (1894).

[23] CORWIN and QUATTLEBAUM, *J. Am. Chem. Soc.*, **58**, 1081 (1936).

Salts are made by fusing pyrrole with sodium or potassium hydroxide. In liquid ammonia,[24] the potassium, sodium, calcium, magnesium, and a number of other derivatives can be prepared. Pyrrylpotassium[25] and carbon dioxide at 200 to 220° give 2- and 3-pyrrole carboxylic acid, a reaction that recalls the familiar Kolbe synthesis. The Reimer-Tieman synthesis of aldehydes from phenols by the use of chloroform and alkali is of limited applicability, the chief reaction being a ring enlargement to β-chloropyridine.[26]

At moderate temperature, metal salts form N-acyl and N-aroyl derivatives[27] with acetyl or benzoyl chloride and the N-methyl compound[28] with methyl iodide. Ethyl iodide gives an N-ethyl product together with some 2-ethyl or 1,2-diethylpyrrole.[29] If these reactions are carried out at higher temperatures (150 to 220°), substitution occurs on a 2- or 3-carbon atom. This result is not necessarily a consequence of a rearrangement of an initially N-substituted product for the temperature at which N-alkyl or acyl derivatives rearrange is usually higher (200 to 270°).

When pyrrole is treated with methylmagnesium iodide, one equivalent of hydrogen is evolved.[30] ~~If the N-pyrrylmagnesium~~ iodide so formed is treated with methyl iodide, the product is largely 3-methylpyrrole with a little of the 2-isomer. Absence of N-methylpyrrole is proved[31] by a test for active hydrogen with ethylmagnesium bromide or metallic potassium. Only pyrroles with N-hydrogen form Grignard reagents, but these N-pyrrylmagnesium halides give C-alkyl products when treated with an alkyl halide. The group enters the 2- or 5-position unless these places are blocked, except in the case of methyl iodide, where the methyl group enters the 3-position. Carbon dioxide and benzoyl chloride likewise yield a C_2-derivative unless blocked there.[32] Ethyl chloroformate gives 1,2-dicarbethoxypyrrole,[33] because the first carbethoxy group makes the imino hydrogen so acidic that an interchange of magnesium from one nitrogen to another occurs during the reaction.

[24] Franklin and Borgstrom, *Chem. Rev.*, **16**, 305 (1935).

[25] Ciamician, *Monatsh.*, **1**, 624 (1880); Ciamician and Silber, *Ber.*, **17**, 1438 (1884).

[26] Bamberger and Djierdjian, *ibid.*, **33**, 536 (1900).

[27] Ciamician and Dennstedt, *ibid.*, **16**, 2348 (1883).

[28] Ciamician and Dennstedt, *ibid.*, **17**, 2944 (1884).

[29] Oddo and Mameli, *Gazz. ital. chim.*, **43**, II, 504 (1913); Hess and Wissing, *Ber.*, **47**, 1416 (1914).

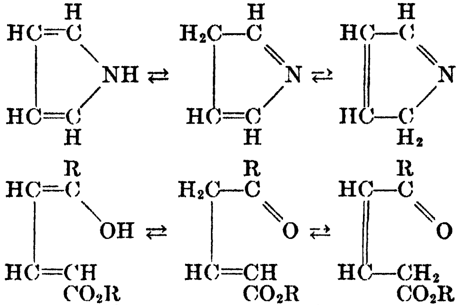
[30] Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909); Gilman and Heck, *J. Am. Chem. Soc.*, **52**, 4949 (1930).

[31] Oddo, *Gazz. chim. ital.*, **44**, I, 706 (1914); *Ber.*, **47**, 2427 (1914).

[32] Colacicchi and Bertoni, *Atti. accad. Lincei*, **21**, II, 450, 518 (1912); *C.A.*, **7**, 1183 (1913).

[33] Signaigo and Adkins, *J. Am. Chem. Soc.*, **58**, 1122 (1936).

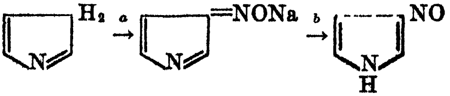
Imine-ketimine System.—Many of the above-mentioned reactions of these magnesium derivatives and indeed of some other organometallic pyrrole compounds are reminiscent of those which occur in the familiar enol-keto tautomerism of the acetoacetate type in which the metal on the oxygen atom forms C- or O-derivatives depending on the reagent employed and on other conditions of the reaction. The complete structural similarity between pyrrole and a hypothetical keto ester with one vinyl group is pictured below. When the sodium salt of ethyl acetoacetate is treated with an alkyl halide, the alkyl group becomes attached to the carbon atom second from the oxygen. If a vinyl radical is introduced in the chain, the alkyl group should become lodged on the fourth carbon from the oxygen atom according to the principle of vinylogy.[34] Similarly, the simplest imine-ketimine change in pyrrole would lead to alkylation at C_3, and this expectation is realized when the alkyl is a methyl group. By the principle of vinylogy, however, the substitution should take place one more vinyl group distant, or at C_5, and this expectation is realized with all alkyl groups except methyl. Viewed in this light, the common alkylation of pyrrylmagnesium halide at C_2 is really a substitution at C_5 or at the end of a vinyl chain. If the 4- and 5-positions are blocked, as in indole, the vinyl chain is shortened and the alkyl groups always enter the 3-positions.



Enimine and enol states

Ketimine and keto states
1,2 change 1,4 change

A tautomeric change is shown also by the reaction of amyl nitrite with pyrrole in the presence of sodium ethoxide. The sodium salt of the isonitroso compound is formed, but on acidification, the nitroso form is recovered. If the system is stabilized by weighting it in the alpha position with a phenyl group—a standard practice, indeed, for isolating an unstable form or for slowing down a change in a tautomeric system—the



---

[a] $C_5H_{11}ONO + NaOEt$. [b] HX.

[34] Fuson, *Chem. Rev.*, **16**, 1 (1935).

free acid can be isolated. The formation of isonitroso-derivative of the analogous acetoacetate compounds has already been mentioned in connection with the Knorr synthesis. Although a hydrogen atom can move readily between nitrogen and carbon in this tautomeric system, and alkyl and other radicals can switch from nitrogen to carbon under thermal impulse, there is no indication that a metal can change in a similar way. Barely more than one equivalent of magnesium from methylmagnesium iodide can be introduced even under strenuous conditions.[30] The formation, therefore, of 2-alkyl derivatives from the reaction of pyrrylmagnesium halide with alkyl halide appears to result from simultaneous changes[35] that involve neither N-alkyl nor C-MgX as intermediate steps. Some formulation similar to that proposed by Michael[36] for the reactions of ethyl acetoacetate or some principle of resonance may offer a convenient picture of the reaction mechanism.

Substitution in the Pyrrole Nucleus.—Substitution occurs readily in pyrroles probably because of the activating influence of the iminophenol group. The ease of substitution is as great as or greater than in phenols; and the directing influence is to the alpha positions, if unoccupied, as would be expected in a phenol. Acetic anhydride at 240 to 250° gives the monoacetyl and the 2,5-diacetyl derivative. If the 2- and 5-positions are blocked, as in 2,3,5-trimethylpyrrole, acetylation, under the influence of aluminum chloride, occurs in the 4-position.[37] Acetonitrile and hydrogen chloride yield a ketimine[38] chlorohydrate, which in turn is hydrolyzed to an acetyl derivative. Similarly, dry hydrogen cyanide and hydrogen chloride, without a catalyst, give the formamido chloride,[39] C_4H_4-N·CH=NH·HCl, which is hydrolyzed by alkalies to the aldehyde. Chloroacetonitrile introduces the acetonitrile group which can be hydrolyzed to the acid.

Such substitutions provide intermediates for the synthesis of many pyrrole derivatives. For example, the aldehyde group forms an unsaturated product with malonic ester, which, by conventional changes, such as hydrolysis or reduction with decarboxylation, can be converted to an acrylic or propionic acid derivative, respectively. Acetyl and formyl substituents are reduced (Wulff-Kizhner) readily to alkyl radicals. Chloroacetonitrile can also be used as a first step for the preparation of an acid by hydrolysis or an amine by reduction.

Pyrroles undergo an unusual reaction when heated with sodium alkoxides at 225°. Hydrogen atoms, acetyl groups, or carbethoxy radicals are replaced by the alkyl of the alkoxide,[40] as shown below. Had sodium methoxide or propoxide been used in the reaction illustrated, the methyl or propyl radicals would have been introduced.

---

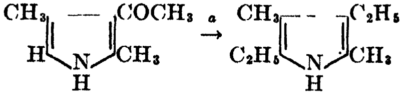
[35] SIDGEWICK, "Chemistry of Nitrogen Compounds," Clarendon Press, Oxford University Press, New York, 1937.

[36] MICHAEL, *Ber.*, **38**, 3217 (1905); PAAL, *ibid.*, **39**, 1436 (1906).

[37] FISCHER and SCHUBERT, *Z. Physiol. Chem.*, **155**, 109 (1926).

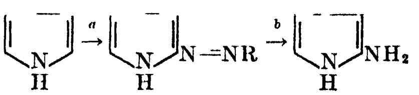
[38] FISCHER, WEISS, and SCHUBERT, *Ber.*, **56**, 1196 (1923).

[39] FISCHER and ZERWECK, *ibid.*, **55**, 1942 (1922).



[a] NaOC$_2$H$_5$ at 225°.

Pyrroles can be coupled with aromatic diazotized amines in the alpha position, or, if the alpha is blocked, the beta position. Reduction of the azo dye with platinum and hydrogen is one of the best preparative methods for aminopyrroles.[41]



[a] RN$_2$X. [b] Reduction.

Nitration and sulfonation are of limited use with pyrroles because of their sensitivity to strong acids. Nitric acid destroys the parent compound, but nitrates pyrroles that have a carboxyl, acetyl, or halogen group.[42] To obtain the mononitropyrrole, advantage may be taken of the formation of the sodium salt of β-nitronic acid, which is prepared from the action of ethyl nitrate and sodium on pyrrole. The nitropyrrole[43] is liberated from the sodium salt by carbon dioxide.

Nitro groups retain the capacity, exhibited in the furan and thiophene series, of displacing other groups besides hydrogen. An acetyl radical is particularly susceptible to removal. For example, 2,4-dimethyl-3-carbethoxy-5-nitropyrrole[44] is formed when concentrated nitric acid attacks 2-4-dimethyl-3-carbethoxy-5-acetylpyrrole. Formyl groups are similarly affected. Methyl groups have sometimes been replaced, while carbethoxy groups remain attached. For example, 2,4-dinitro-3,5-carbethoxypyrrole[44] results from the nitration of 2,4-dimethyl-3,5-dicarbethoxypyrrole.

Sulfonation with concentrated sulfuric acid is impractical, but chlorosulfonic acid may be used. As usual, the action of such a strong agent is best accomplished when a carbethoxy group is already present in the molecule, as witnessed by the conversion of 3,5-dimethyl-2-carbethoxypyrrole to 3,5-dimethyl-2-carbethoxypyrrole-2-sulfonic acid.[45]

---

[40] Fischer and Rose, *Z. physiol. Chem.*, **87**, 38 (1913); Fischer and Bartholomäus, *ibid.*, **80**, 6 (1912); Colacicchi and Bertoni, *Atti. accad. Lincei*, **21**, I, 653, II, 450, 518; CA **7**, 1183 (1913).

[41] Fischer and Hepp, *Ber.*, **19**, 2251 (1886); Fischer and Rothweiler, *ibid.*, **56**, 512 (1923).

[42] Ciamician and Silber, *ibid.*, **18**, 1456 (1885); **19**, 1078 (1886).

[43] Angeli and Alessandri, *Atti accad. Lincei* [1], **20**, 311 (1911); *C.A.*, **5**, 3403 (1911); Angeli, *Ber.*, **57**, 834 (1924).

[44] Fischer and Zerweck, *ibid.*, **55**, 1949 (1922).

Halogenation proceeds with vigor. Chlorine produces an unstable tetrachloride, but the milder acting sulfuryl chloride in ether at zero degrees gives a mono alpha product.[46] The 2-methyl group is readily substituted also as shown by formation of 5-hydroxy-2(trichloromethyl)-4-methyl-3-carbethoxypyrrole[47] from 5-hydroxy-2,4-dimethyl-3-carbethoxypyrrole.

Bromine likewise forms a tetrabromopyrrole. Substituted pyrroles can be brominated, even to replacement of an acetyl group.[48] Side-chain bromination occurs also, as illustrated by the formation of 2(bromomethyl)-4-methyl-3-bromo-5-carbethoxypyrrole from 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole. If bromine is allowed to react with ammonia or potassium thiocyanate in the presence of a pyrrole, the bromothiocyanate (BrSCN) so formed causes introduction of the thiocyano group[49] in either the alpha or beta position.

So readily does substitution occur that tetraiodopyrrole is formed from pyrrole and iodine–potassium iodide solution. The product is called Iodol[50] and is used therapeutically for the same purpose as is iodoform.

Chloromethyl or bromomethyl groups can be converted to aldehydes by way of an anil.[51] Dichloro- or dibromo-methyl groups can be hydrolyzed to an aldehyde.

$$PCH_2Br \xrightarrow{a} PCH_2NHC_6H_5 \xrightarrow{b} PCH{=}NC_6H_5 \xrightarrow{c} PCHO$$

P = pyrryl residue.
^{a} $C_6H_5NH_2$. ^{b} $KMnO_4$, $PbNO_3$, or CrO_3. ^{c} H_2O + HX.

A large excess of sulfuryl chloride or bromide will introduce[52] a halogen atom on the pyrrole ring. This reaction is common in the dipyrrylmethene preparation described in the next chapter.

Addition Reactions.—Triphenylmethyl adds across the butadiene system of pyrrole and yields 2,5-bis(triphenylmethyl)pyrroline[53] in the same way that it adds to isoprene. Since maleic anhydride forms 2-pyrrolesuccinic acid,[54] the triphenylmethyl reaction is a more sensitive test for diene character in this instance than is the familiar Diels-Alder reaction.

---

[45] PRATESI, *Gazz. chim. ital.*, **65**, 43 (1935).

[46] MAZZARA and BORGO, *ibid.*, **35**, I, 477 (1905); MAZZARA, *ibid.*, **32**, II, 315 (1902).

[47] FISCHER and ADLER, *Z. physiol. Chem.*, **197**, 269 (1931).

[48] FISCHER and SCHEYER, *Ann.*, **434**, 237 (1923); FISCHER and BARTHOLOMÄUS, *Z. physiol. Chem.*, **87**, 255 (1912).

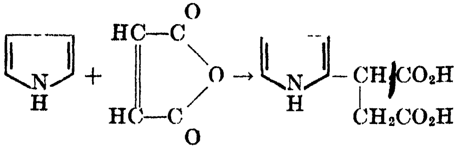
[49] KAUFMANN and OEHRING, *Ber.*, **59**, 187 (1926).

[50] CIAMICIAN and DENNSTEDT, *ibid.*, **15**, 3582 (1882); CIAMICIAN and SILBER, *ibid.*, **18**, 1766 (1885); **19**, 3027 (1886).

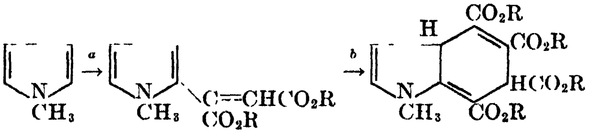
[51] FISCHER and ERNST, *Ann.*, **447**, 139 (1926).

[52] FISCHER, STURM, and FRIEDRICH, *ibid.*, **461**, 244 (1928).

[53] CONANT and CHOW, *J. Am. Chem. Soc.*, **55**, 3475 (1933).



Acetylenedicarboxylic ester behaves as does maleic anhydride, but in this case, a reactive diene system is created which reacts normally with a second molecule of the ester. Proof[55] of these steps is given by bromine oxidation, hydrolysis, and decarboxylation of the product to the known N-methylindole. The dicarboxylic ester also adds to two pyrrole nuclei to form the dipyrrylsuccinnic acid derivative $PCH_2(CO_2R)CH_2(CO_2R)P$ where P is the N-methylpyrrole.



[a] Methyl acetylenedicarboxylate. 1,2-Addition. [b] Methyl acetylenedicarboxylate. 1,4-addition.

Reduction of pyrroles may be partial or complete. Zinc dust and acetic or hydrochloric acid generally put hydrogen in the 2,5- positions (1,4 addition to a diene) to yield a Δ^3-pyrroline.[56]

Δ^2-Pyrrolines occasionally result by reduction, but usually must be obtained by synthesis. Reduction with red phosphorus[57] and hydriodic acid or with catalytic hydrogen over platinum oxide[58] or nickel[33] gives the tetrahydro (pyrrolidine) compound. Pyrrolidines are obtained also by reduction of lactones and succinimides with sodium and boiling amyl alcohol[59] or electrolytic hydrogen.[60]

When hydrogen chloride is passed into an ethereal solution of pyrrole, a tripyrrole, $(C_4H_5N)_3\cdot HCl$, precipitates, which is isolable as the ferricyanide complex.[61] After many days in cold acid, an amorphous orange red material, called "pyrrole red," forms. The composition[62] of this product is unknown. Unilaterally substituted pyrroles form dimers. Steps patterned on a diene addition mechanism have been proposed for this reaction. Such dipyrroles[63] may be distilled unchanged or converted to indoles by loss of ammonia. Otherwise they are depolymerized by heat. They form salts with acids and methiodides, reactions that are practically unknown with pyrroles. A dihydropyrrole unit may, therefore, be present.

---

[54] Diels and Alder, *Ann.*, **490**, 267 (1931).

[55] Diels and Alder, *ibid.*, **490**, 267 (1931); **498**, 1 (1932).

[56] Ciamician, *Ber.*, **37**, 4244 (1904); Willstätter and Hatt, *ibid.*, **45**, 1477 (1912).

[57] Knorr and Rabe, *Ber.*, **34**, 3498 (1901).

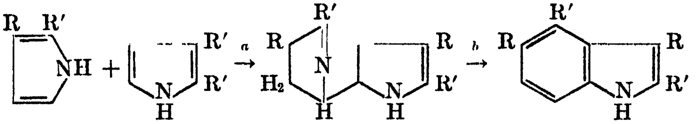
[58] Putokhin, *J. Russ. Phys. Chem. Soc.*, **62**, 2216 (1930); CA **25**, 3995 (1931).

[59] Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, p. 323, Academische Verlagsgesellschaft m.b.H., Leipsig, 1934.

[60] Spath and Breusch, *Monatsh.*, **50**, 349 (1928).

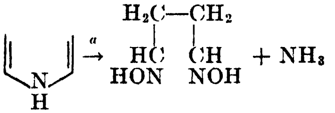
[61] Fischer and Orth, *op. cit.*, p. 24.

[62] Fischer and Bartholomäus, *Z. physiol. Chem.*, **83**, 50 (1913).



[a] HX in dry ethereal solution. [b] H_2SO_4 causes loss of ammonia.

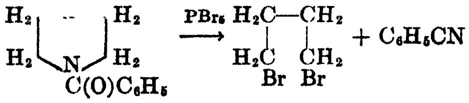
Ring Opening.—The cyclic imide character of pyrroles suggests the possibility of ring opening by aqueous alkali, and the simultaneous presence of hydroxylamine permits fixation of the dialdehyde product as the dioxime.[64] Alkyl groups facilitate this cleavage. Phenyl, acyl, and carboxyl groups retard and sometimes stop the reaction. Hydroxylamine is unnecessary in the case of pyrrole-2,5-dipropionic acid,[65] the diketone from which is stable.



OH in the presence of H_2NOH.

Ring opening by acid, as in the furan series, is not in general possible with the pyrroles. A very few compounds, such as 2-hydroxy-3,5-dimethyl-4-carbethoxypyrrole[66]—this compound can, however, be considered as a lactam also—can be opened by this agent.

Pyrroles can be reduced to pyrroline and pyrrolidines and then converted to the benzoyl derivative. On treatment with phosphorus pentabromide, benzonitrile is eliminated and the corresponding dibromide formed. The reaction is a preparative method for dibromides.



---

[63] ALLEN, GILBERT, and YOUNG., *J. Org. Chem.*, **2**, 235 (1937).

[64] CIAMICIAN, *Ber.*, **37**, 4200 (1904).

[65] DIELS and ALDER, *Ann.*, **486**, 221 (1931).

[66] FISCHER and MÜLLER, *Z. physiol. Chem.*, **132**, 74 (1922); DUDEN and HEYNSIUS, *Ber.*, **34**, 3054 (1901).

Pyrroles are readily oxidized to succinimides[67] by chromic oxide in sulfuric acid. This method is valuable in the determination of structure, because the corresponding maleic acid can be prepared independently. If bromine water is employed as the oxidizing agent, the product is dibromomaleic imide. Nitric acid and lead dioxide have also been used. Air in the presence of light and moisture forms succinimides.

Tests for Pyrroles.—The earliest test for pyrroles was the fiery red color produced on a pine splinter moistened by hydrochloric acid. The intensity and shade varies with the compound tested. The color is caused by aldehydes present in the wood which combine with pyrroles which have a free methine group.[68] 1,4-Dimethyl-3,5-diethylpyrrole and other tetra-substituted compounds give no coloration. The action is not specific for pyrroles, since indoles and methyl homologues of furan respond positively.[69]

This pine-splinter test has been used to show the presence of pyrrole-forming products, probably levulinic acid, in rubber. If oxidized or aged rubber is heated carefully with fused ammonium acetate and then distilled with steam, the distillate will give a positive test. The determination is made quantitative by comparison of the color with a set of standards.[70]

Ehrlich[71] noticed that certain samples of urine gave an intense red color with *p*-dimethylaminobenzaldehyde. This reaction is caused by the presence of pyrroles and is given by all pyrroles[72] with an unsubstituted alpha position. Tetrasubstituted pyrroles with an ester or carboxyl group in the alpha position will develop the color when heated. The reaction is partially successful with compounds that have a free beta position. Since phloroglucinol, pyrogallol, orcinol, and resorcinol also show the Ehrlich test, their absence must be ensured.

The characteristic absorption bands produced in the Ehrlich test are the same as those shown by certain dipyrrylmethane[73] compounds and by some pyrrylphenylmethanes. Among the latter is the yellow product, pictured below, which can be isolated as a crystalline salt. When treated with dilute acid, it becomes red; with concentrated acid it becomes colorless. The result suggests the structure of the colored compound in the Ehrlich test. Phthalic anhydride forms either a pyrrolen-

---

[67] PLANCHER and CATTADORI, *Atti accad. Lincei*, **13**, I, 489 (1904); *Chem. Zentr.*, II, 305, (1904).

[68] ERDMANN AND ERDMANN, *Ber.*, **32**, 1218 (1899); **35**, 1859 (1902).

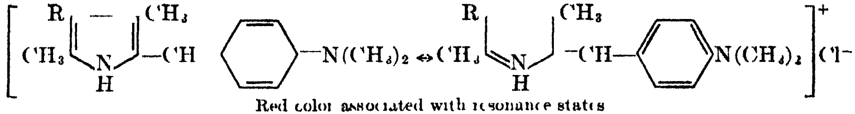
[69] REICHSTEIN, *Helv. Chim. Acta*, **15**, 1110 (1932).

[70] TEMPLE, CADWELL, and MEAD, JR., *Ind. Eng. Chem., Anal. Ed.*, **2**, 377 (1930).

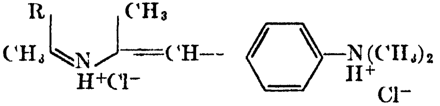
[71] EHRLICH, *Med. Woche*, 151 (1911).

[72] FISCHER and ORTH, "Die Chemie des Pyrrols," Vol. I, Academische Verlagsgesellschaft, m.b.H., Leipzig, 1934.

[73] FISCHER and ADLER, *Z. physiol. Chem.*, **197**, 237 (1931).



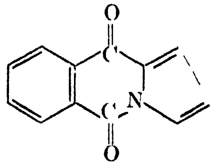
Red color associated with resonance states

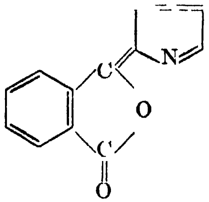


Colorless product

R = $-CH_2CH(CO_2H)_2$

phthalide or its desmotrope.[74] These compounds may be used to char-

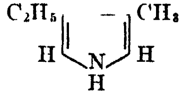




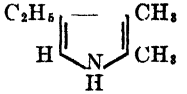
acterize pyrroles that are appropriately constituted for reaction with the anhydride.

Pyrroles, tetra-substituted ones excepted, form products with mercuric chloride, which, in some cases, have the composition $(pyrrole)_2Hg(HgCl_2)_4$.[75] The pyrrole can be recovered from the hot aqueous acid suspension of the salt by treatment with hydrogen sulfide. Picric, chloropicric, styphnic, and picrolonic acids combine readily with pyrroles; because of the sharp melting points, the products are valuable for identification. Pyrroles can also be heated at 120° with arsenic acid in order to obtain solid derivatives.[75]

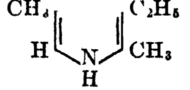
Pyrrole Compounds.—Apart from pyrrole itself, the best known simple pyrrole compounds are those which come from the molecule of chlorophyll or hemin or are used in the synthesis of such substances. *Opso-*, *hemo-*, *crypto-*, and *phyllo-pyrrole* have been obtained by reduction of these natural products with hydroiodic acid.



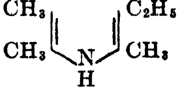
Opsopyrrole or 3-methyl-4-ethylpyrrole



Hemopyrrole or 2,3-dimethyl-4-ethylpyrrole



Cryptopyrrole or 2,4-dimethyl-3-ethylpyrrole



Phyllopyrrole or 2,4,5-trimethyl-3-ethylpyrrole

---

[74] Fischer and Orth, *Ann.*, **502**, 238 (1933).

[75] Fischer and Müller, *Z. physiol. Chem.*, **148**, 155 (1925).

Bilirubin by a similar method yields hemo- and crypto-pyrrole. The common names designate either the source or some fact connected with the discovery of the compound. Hemopyrrole is so named because it is the principal pyrrole in hemin; opsopyrrole, from the Greek word ὀψέ, meaning "late," refers to its discovery at a later period among the decomposition products of hemin; cryptopyrrole, from χρυπτος meaning "hidden," is intended to recall the difficulty met in finding it; phyllopyrrole indicates that it was derived from chlorophyll.

TABLE I.—PHYSICAL CONSTANTS OF SOME PYRROLE COMPOUNDS

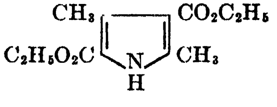
Pyrrole	M.p., °C.	B.p., °C.	Pressure, mm.
N-Methyl-	.....	114–115	
2-Methyl-	.....	149	760
3-Methyl-	.....	45	11
2,3-Dimethyl-	.....	65	14
2,4-Dimethyl-	.....	162–164	720
2,5-Dimethyl-	.....	165	780
3,4-Dimethyl-	33[a]	65–66	14
N-Acetyl-	[b]	180–181	
2-Acetyl-	90	218–220	760
3-Nitro-	63.5		
Hemo-	13	87–88	12
Crypto-	.....	86	11
Phyllo-	69	86–87	12
Opso-	3	73–75	13
Knorr's	136		
2,5-Dihydro-	.....	90–91	748
Tetrahydro-	.....	87	

[a] Note lower melting point of N-substituted pyrroles in agreement with their role as ammono ethers.

[b] Note lower melting points of the less symmetrical isomers.

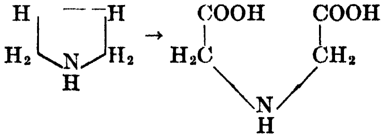
Designs for preparations of these compounds are very simple and can be proposed by anyone familiar with the Knorr synthesis. Any pyrrole compound that contains a methyl group in both the 2- and 4-position can be derived from Knorr's pyrrole (see below) by suitable changes imposed on the two carbethoxy groups. Any compound such as hemopyrrole that contains a methyl group at C_2 but not at C_4 can be made with the help of ethyl acetoacetate as one of the components in a Knorr synthesis. The other component is an appropriate ketone. If hydrogen only is in the alpha position, as in pyrrole, oxalacetic ester can be used as one unit because the carbethoxy group can be hydrolyzed and then eliminated readily. The other portion would be an appropriate ketone such as ethyl methyl ketone, which forms an isonitroso compound. In devising syntheses for these or any other compounds, the special role of carbethoxy as a blocking group that can subsequently be removed (hydrolysis and decarboxylation) or substituted (hydrolysis and acylation, alkylation with alkoxides, or nitration) must be remembered. Many condensations are facilitated also by the presence of this group.

Knorr's pyrrole is 2,4-dimethyl-3,5-dicarbethoxypyrrole. It was obtained by Knorr from ethyl acetoacetate in his discovery of the synthesis that bears his name. It is capable of a wide number of transformations.



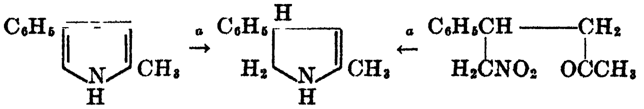
By treatment with sulfuric acid below 40° the β- but not the α-carbethoxy group is hydrolyzed to give 2-carbethoxy-3-5-dimethylpyrrole-4-carboxylic acid.[23] The latter in turn can be decarboxylated with quinoline and copper. Sulfuric acid at higher temperatures hydrolyzes both carbethoxy groups. Hence substitution in the 3- and 5-positions can be made separately or simultaneously. By chlorination of the methyl groups and hydrolysis, aldehydo derivatives can be obtained. Reduction and ring opening yields noncyclic compounds.

Δ^3 *Pyrroline* is the dihydro reduction (zinc or iron with acetic acid) product of pyrrole. The position of the double bond is proved by the isolation of imino-diacetic acid after oxidation of the ozonide[76] with hydrogen peroxide.



In contrast to pyrrole, Δ^3 pyrroline is a strong base with an ammoniacal odor and is very soluble in water.

Not all reductions lead to an α Δ^3 compound. The position of the double bond is determined by the nature of the substituents present. A Δ^2 product, for example, is formed from 2-methyl-4-phenylpyrrole.[76b] The constitution is proved by synthesis from methyl-γ-nitro-β-phenyl-*n*-propyl ketone.



[a] Zn + HOAc. The nitro compound is made by addition of sodium nitromethane to benzalacetone.

[76] Treibs and Dinelli, *Ann.*, **517**, 170 (1935); Sonn, *Ber.*, **68**, 148 (1935).

Proline is α-pyrrolidene carboxylic acid. With hydroxyproline it is widely distributed among proteins. Unlike the majority of amino acids, these two compounds do not liberate nitrogen when treated with sodium nitrite. Therefore, measurement of the nonamino nitrogen in the filtrate after precipitation with phosphotungstic acid and combination of the results with those obtained from a fractional extraction of protein hydrolyzate with butyl and propyl alcohol, and also comparison of the values with a precipitation of the proline with cadmium chloride (hydroxyproline is not precipitated), give a very accurate estimation[77] of the quantity of these products in proteins. Gelatin contains 9 and 14 per cent, respectively, of proline and hydroxyproline; casein contains 5.7 and 2.1 per cent of each compound; zein has 8.4 and 0.8 per cent, respectively. The N-methylation product of proline is known as "stachydrine."

Synthesis of *d,l*-proline from pyrrole is effected by treatment of pyrrole in sequence with ethylmagnesium bromide, chloroethyl formate, ethylmagnesium bromide, chloroethyl formate, hydrogen[33] over Raney nickel or platinum oxide to give 1,2-dicarbethoxypyrolidine. The *d, l*-proline is obtained by heating this dicarboxylic ester with hydrochloric acid for 5-hr.

Several methods of synthesis of proline from propylene dibromide have also been devised. For example, the dibromide and ethyl malonate, under the influence of sodium ethoxide, give $\mathrm{Br(CH_2)_3CH(COOEt)_2}$. Bromination then replaces the hydrogen adjacent to the carbethoxy groups with a halogen atom, and the resulting dibromide is converted to a ring structure, $\mathrm{H\overline{N(CH_2)_3C}(CONH_2)_2}$, by ammonia. Hydrolysis by hydrochloric acid with concurrent loss of one molecule of carbon dioxide completes the synthesis.[78] Another process replaces the bromine atom on one end of propylene dibromide by a phthalimido group and on the other end by a malonyl ester, to form the product $\mathrm{C_6H_4(CO)_2{-}N(CH_2)_3CH(COOR)_2}$. Bromination then inserts a halogen atom on the malonyl end, and alcoholic ammonia at 100°[79] converts the product to a pyrrolidine compound. Finally, trimethylene bromide may be combined with sodiophthaliminomalonic ester to form $\mathrm{Br(CH_2)_3C(CO_2R)_2{-}N{\cdot}C_8H_4O_2}$ and the product then made to undergo ring closure[80] under the influence of alcoholic sodium hydroxide.

Proline may also be prepared from α-piperidone[81] by a sequence of chlorination, ring opening, hydrolysis, and ring closure with reduction as shown below.

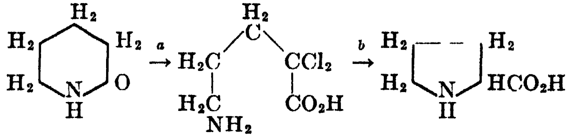
[77] Fürth and Minnibech, *Biochem. Z.*, **250**, 18 (1932).

[78] Willstätter and Ettlinger, *Ann.*, **326**, 91 (1903).

[79] Fischer, *Ber.*, **34**, 454 (1901).

[80] Sorensen and Andersen, *Z. physiol. Chem.*, **56**, 236 (1908).

[81] Heymons, *Ber.*, **66**, 846 (1933).



[a] PCl_5, Cold soda solution to liberate free base. [b] NaHg.

Problems

1. What are the products formed when the following substances are subjected to the conditions indicated? (*a*) Aniline and mucic acid distilled together;[82] saccharic acid and isoamylamine distilled together in a vacuum at 70°. (*b*) α-Aminopyridine and mucic acid heated to 225° with aluminum oxide.[83] (*c*) Phenacylacetoacetic ester and *p*-nitroaniline.[84] (*d*) Phenacylacetoacetic ester and benzidine.[10b] (*e*) Acetonylacetone and ammonium carbonate heated together in an oil bath at 100° until effervescence ceases. (*f*) Tetramethylene dibromide and 2-methyl-5-ethylpiperidine.[85] (*g*) β-Keto-γ-aminobutane chlorohydrate, $CH_3C(O)CH(NH_2)CH_3{\cdot}HCl$, and ethyl methyl ketone in the presence of caustic potash; the same ketoamino compound with oxalacetic ester.[15b] (*h*) *m*-Phenylenediamine allowed to stand with acetophenoneacetoacetic ester in acetic acid for a long time.[10b]

2. Start with ethyl acetoacetate and prepare the following: (*a*) 2,4-Dimethyl-5-carbethoxypyrrole; 2,4-dimethyl-5-carbethoxy-3-aldehydopyrrole; 2,4-dimethyl-5-carbethoxy-pyrrole-3-acrylic acid; 2,4-dimethyl-5-carbethoxy-3-vinylpyrrole in a sequence of reactions.[86] (*b*) 1,2,4-Trimethyl-5-carbethoxypyrrole; 1,3-dimethyl-2,4-dicarbethoxy-5-aldehydropyrrole; 1,3,5-trimethyl-2-carbethoxy-4-acetylpyrrole; N-methyl methylethylmaleic imide.[23] (*c*) 2,4-Dimethylpyrrole.[87] (*d*) 2,4-Dimethyl-3,5-diethylpyrrole.[68] (*e*) 2,4-Dimethyl-3-propylpyrrole.[89] (*f*) 2,4-Dimethylchloroacetylpyrrole.[88] (*g*) 2-Bromomethyl-4-methyl-3,5-dicarbethoxypyrrole.[90] (*h*) 4-Amino-2,5-dimethyl-3-carbethoxypyrrole.[91] (*i*) 2,4-Dimethyl-5-carbethoxypyrrole-3-propionic acid and then brominate the product.[72]

3. How would you condense the following? (*a*) Isonitrosoacetoacetic ester with acetylacetone to obtain a pyrrole compound and from thence obtain kryptopyrrole or phyllopyrrole.[92] (*b*) Acetylpyruvate with an aminobutanone to form a pyrrole compound and from thence proceed to hemopyrrole or phyllopyrrole.[15a] (*c*) Acetylpyruvate with aminoacetone to obtain a pyrrole compound and from thence obtain opsopyrrole.[52]

---

[82] KÖTTNITZ, *J. prakt. Chem.*, **6,** 136 (1872); PICTET and STEINMANN, *Ber.*, **35,** 2529 (1902); REICHSTEIN, *Helv. Chim. Acta*, **10,** 389 (1927).

[83] TSCHITSCHIBABIN and BYLINKEN, *Ber.*, **58,** 1745 (1923); WIBAUT and DINGEMANSE, *Rec. trav. chim.*, **42,** 1039 (1923).

[84] BORSCHE and TITSINGH, *Ber.*, **40,** 5008 (1907).

[85] v. BRAUN, LEMKE, and NELKEN, *ibid.*, **56,** 1564 (1923).

[86] FISCHER and BARTHOLOMÄUS, *Z. physiol. Chem.*, **77,** 190 (1912).

[87] FISCHER and HIERNEIS, *Ann.*, **492,** 32 (1931).

[88] PILOTY, *Ber.*, **43,** 489 (1910); FISCHER and BARTHOLOMÄUS, *Ber.*, **45,** 466, 1984 (1928).

[89] FISCHER, GOLDSCHMIDT, and NÜSSLER, *Ann.*, **486,** 14 (1931).

[90] FISCHER and HALBIG, *ibid.*, **447,** 129 (1926).

[91] FISCHER and ROTHWEILER, *Ber.*, **56,** 516 (1923).

[92] KNORR and HESS, *ibid.*, **44,** 2758 (1914); FISCHER and SCHUBERT, *ibid.*, **57,** 610 (1927). See also reference 72, p. 55.

4. Name the product of the reaction of the following: (*a*) 2,4-Dimethylpyrrole heated with sodium ethoxide at 220°.[86] (*b*) 2,5-Dimethyl-3,4-dicarbethoxypyrrole heated for 16 hr. with sodium ethoxide at 220°.[40] (*c*) N-Methyl-2,4-dimethyl-3,5-dicarbethoxypyrrole in contact with two molecular proportions of sulfuryl chloride in acetic acid, followed by hydrolysis of the product.[23] (*d*) 3-Ethyl-2,4-dimethylpyrrole with benzenediazonium chloride.[93] (*e*) 2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole and nitric acid.[39] (*f*) Pyrrylmagnesium bromide and phthalyl chloride.[94]

5. Analysis of a certain pyrrole shows that it is an ethyltrimethylpyrrole. How would you show that the nitrogen atom is or is not substituted and, if so, how would you determine whether a methyl or ethyl group is attached to the nitrogen atom?[23]

6. The reaction of methyl iodide on pyrrylmagnesium iodide forms 3-methylpyrrole, that of ethyl iodide leads largely to the 2-ethylpyrrole. How would you determine the location of these substituents?[95]

7. Triphenylmethyl and pyrrole form a dihydro derivative. How would you show that addition is in the 2,5-position?[53]

8. Devise a method for the preparation of 5-bromo-4-methyl-3-ethyl-2-aldehydopyrrole.[96]

9. Show a method for preparing α,β-dichloroethyl ether and for condensing it with diacetonitrile (cyanoacetone) in the presence of ammonia (the dichloro compound is merely a convenient way of obtaining chloroacetaldehyde *in situ*). How would the pyrrole product[97] react with (*a*) bromine (*b*) hydrogen cyanide and hydrochloric acid?

10. Devise a method for preparing 2-methylpyrrole, then 2-methyl-3-formyl-5-carbethoxypyrrole, and finally for conversion to 2,3-dimethylpyrrole.[98] Devise a method for preparing 2-5-dimethylpyrrole.[99]

11. Ikterogen[72] is a physiologically active compound known scientifically as 2,4-dimethylpyrrole-1-arsinic acid, $C_6H_9N \cdot HAsO_3$. Devise a method for its synthesis from arsanilic acid as one of the reagents.

12. The structure of β-nitropyrrole has been proved by synthesis from sodium nitromalonic aldehyde and the ethyl ester of glycine. Write the equations for the synthesis of the malonic aldehyde from mucobromic acid and sodium nitrite and for condensation of this dialdehyde with the amino compound.[100]

13. 4,6-Di(2,5-dimethyl-3-carboxypyrrole)-1,3-dimethylbenzene, $(CH_3)_2C_6H_2$-$[NC_4H(CH_3)_2CO_2H]_2$ was prepared as part of a study of isomerism by restricted rotation.[101] Write the formula of the compound. What intermediate compounds would be needed to effect a synthesis? How could the two necessary intermediates be prepared? How many isomers would result?

---

[93] Fischer and Hepp, *ibid.*, **19,** 2251 (1886); Fischer and Bartholomäus, *Z. physiol. chem.*, **77,** 193 (1917).

[94] Bernado and Francesco, *Gazz. ital. chim.*, **53,** 265 (1923).

[95] Oddo and Mameli, *ibid.*, **43,** II, 504 (1913); *C.A.*, **8,** 1272 (1914).

[96] Siedel and Fischer, *Z. physiol. Chem.*, **214,** 158 (1933).

[97] Strain, *Ann.*, **499,** 40 (1932).

[98] Fischer, Belles, and Stern, *Ber.*, **61,** 1081 (1928).

[99] Paal, *ibid.*, **18,** 2251 (1885); Knorr, *Ann.*, **236,** 290 (1886).

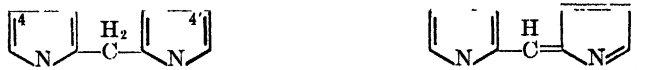
[100] Hill and Torrey, *Am. Chem. J.*, **22,** 89 (1899); Hale and Hoyt, *J. Am. Chem. Soc.*, **37,** 2538 (1915).

[101] Chang and Adams, *ibid.*, **56,** 2089 (1934).

CHAPTER V

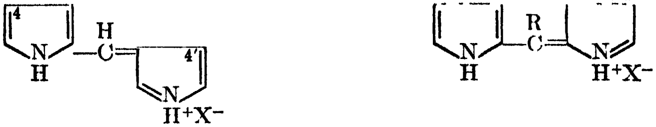
DI- AND POLY-PYRRYL COMPOUNDS. PORPHYRINS AND PHTHALOCYANINS

Two pyrrole nuclei can be joined to each other through a carbon atom to give a dipyrrylmethane analogous to diphenylmethane, or a dipyrrylmethene; two such methane or methene units can be joined to make bilirubins, porphyrins, and phorbins. The chemistry of dipyrrylmethanes and -methenes is, therefore, important because of the role that such substances have as intermediates in the synthesis of compounds related to many that occur in nature.



α,α′-Dipyrromethane or pyrromethane

α,α′-Dipyrromethene or pyrromethene hydrohalide

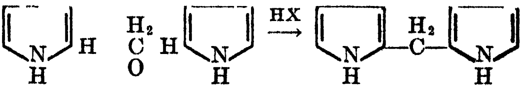


α,β′-Pyrromethene hydrohalide

ms R-dipyrromethene hydrohalide

FIG. 1.—Typical naming and numbering of the dipyrromethanes and methenes.

Dipyrrylmethanes.—Dipyrrylmethanes, sometimes referred to as pyrromethanes, can be prepared by a number of methods. Methylene chloride and pyrrylpotassium at 120 to 130° give α,α′-dipyrrylmethane, together with much of the N,N′-isomer;[1] hydrazine and sodium ethoxide at 165° reduce dipyrryl ketones[2] which are previously prepared by a Friedel-Crafts synthesis between a pyrrole and a pyrrole acid chloride or phosgene; and formaldehyde condenses with an alpha-free pyrrole[3] in the presence of formic or a mineral acid with formation of a dipyrrylmethane.



---

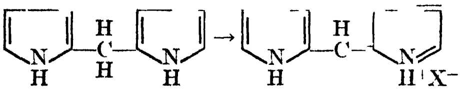
[1] PICTET and RILLIET, *Ber.*, **40**, 1166 (1907).

[2] HESS and ANSELM, *ibid.*, **54**, 2310 (1921).

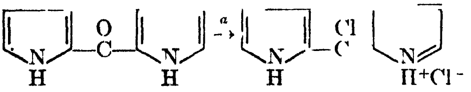
[3] (*a*) FISCHER and ZEILE, *Ann.*, **462**, 210 (1928); (*b*) CORWIN and QUATTLEBAUM, JR., *J. Am. Chem. Soc.*, **58**, 1081 (1936).

This last reaction is common. Should the alpha positions be blocked, a β,β'-dipyrrylmethane[4] can form. α,β'-Dipyrrylmethanes, mixed with other products of course, are obtained from an alpha-free pyrrole with an appropriate beta-free compound. Replacement of formaldehyde by acetaldehyde or benzaldehyde or even by ketones leads to the corresponding *ms.*-substituted pyrrylmethane.[5] Glyoxal gives the expected tetrapyrrylethane.[6] This type of condensation is capable of wide variation.

Mild oxidation of dipyrromethanes with ferric chloride, chloroanil, or bromine changes them to dipyrromethenes. If the methane has an α-carbethoxy group, however, ferric chloride changes it to a tetrapyrrylethane.[7]



Dipyrrylmethenes.—Besides the aforementioned oxidation of the methane, dipyrrylmethenes can be prepared from a ketone by a novel reduction with phosgene. Carbon dioxide is eliminated and a chloro product[8a] results. The reaction has its parallel in the aromatic series in the behavior of ketones with oxalyl chloride,[8b] in which a dichloride is formed and carbon monoxide and carbon dioxide are evolved.



[a] $C(O)Cl_2$. The reaction probably proceeds through the intermediate dichloro compound, $PyC(Cl_2)Py$, followed by loss of HCl.

The usual synthesis, however, is to condense an appropriately substituted aldehydopyrrole with another alpha-free pyrrole or to link alpha-free pyrroles together by the use of formic acid or chloromethyl ether[9] (see Fig. 2). Pyrroles with alkyl groups only in the beta position have a great tendency to form methenes.[10]

When an alpha-free α'-methylpyrrole is treated with cold bromine, or, better, with sulfuryl chloride, a dihalogeno product forms, which then condenses with some of the unhalogenated pyrrole and forms a dipyrrylmethene. The reaction is illustrated by the formation of 5-chloro-4,3′,5′-trimethyl-3,4′-diethyldipyrromethene hydrochloride[11]

---

[4] Colocicchi, *Atti, accad Lincei*, [5] **20**, II, 312 (1911); *Chem. Zentr.*, I, 143, (1912).

[5] Fischer and Bartholomäus, *Z. physiol. Chem.*, **89**, 163 (1913).

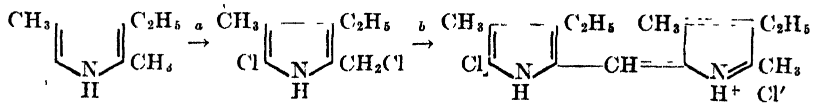
[6] Fischer and Eismeyer, *Ber.*, **47**, 2019 (1914).

[7] Fischer, Baumgartner, and Plötz, *Ann.*, **493**, 1 (1932).

[8] (*a*) Fischer and Orth, *ibid.*, **489**, 62 (1931); **502**, 237 (1933); (*b*) Staudinger, *Ber.*, **42**, 3966 (1909).

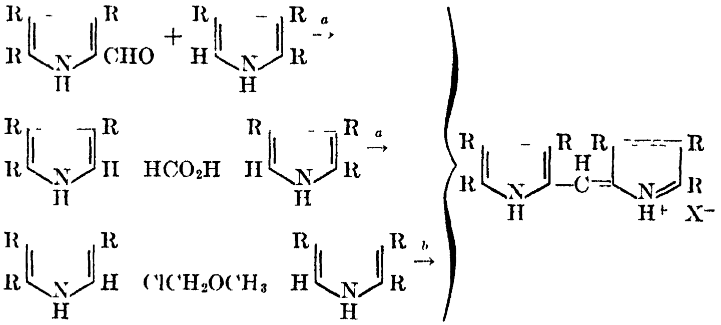
[9] Fischer and Zerweck, *ibid.*, **56**, 519 (1923); Fischer and Adler, *Z. physiol. Chem.*, **197**, 252 (1931).

[10] Fischer, Doyle, and Gleim, *Ann.*, **525**, 24 (1936).



[a] $SOCl_2$. [b] Reaction with the cryptopyrrole used as the starting material.

from cryptopyrrole. Any acetyl group present in the original pyrrole may be replaced by a chlorine atom[12] during the process, subject of course to thermal influence.



[a] HBr or HCl. [b] Hot benzene or alcohol solution.

FIG. 2.—Methods for the synthesis of dipyrromethenes.

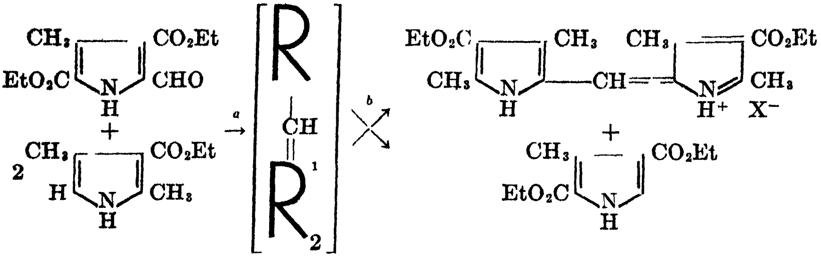
In the aromatic series, the condensation of an aromatic aldehyde with a ring system that contains an active hydrogen atom produces a triarylmethane as, for example, in the formation of malachite green from benzaldehyde and dimethylaniline. In the pyrrole series, the condensation of a pyrrolaldehyde with the active hydrogen of a pyrrole ring produces a dipyrrylmethene. There are some instances, however, where, at low temperature, when the period is short, or the agent is heat instead of an acid, a tripyrrylmethane[13] results. Since hydrochloric, hydrobromic, or formic acid readily cleave such compounds to dipyrrylmethenes, it is possible that tripyrrylmethanes may often be intermediate products. Indeed certain anomalous condensations such as the one that follows are best explained by such a mechanism.

---

[11] FISCHER, BAUMANN, and RIEDL, *ibid.*, **475**, 205 (1929).

[12] FISCHER and ADLER, *Z. physiol. Chem.*, **210**, 148 (1932).

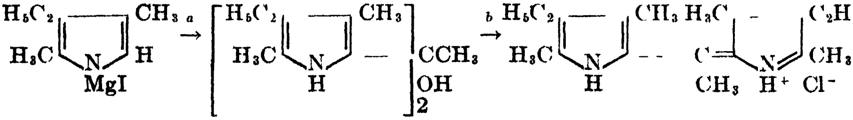
[13] FISCHER and ERNST, *Ann.*, **447**, 139 (1926); FISCHER and AMMANN, *Ber.*, **56**, 2319 (1916); CORWIN and ANDREWS, *J. Am. Chem. Soc.*, **58**, 1086 (1936); **59**, 1973 (1937).



Large R = the dicarbethoxypyrryl radical, large R¹ = the monocarbethoxypyrryl radical.
ᵃ HCl. ᵇ HCO₂H.

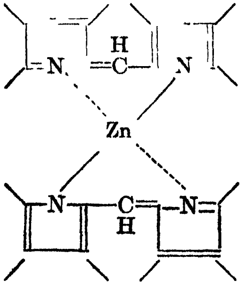
FIG. 3.—Abnormal condensation in which the unit of the pyrrole aldehyde is not part of the final dipyrrylmethene product. Some of the expected product is of course formed in this reaction, particularly if excess aldehyde and hydrochloric acid is used.

So also does the reaction of acetyl chloride with cryptopyrrylmagnesium iodide produce the expected tertiary carbinol, but the product loses water and changes to 3,5,3′,5′-tetramethyl-4,4′-diethyl-*ms*.-methyldipyrromethene hydrochloride.[14]



ᵃ CH_3COCl. ᵇ HCl.

Dipyrrylmethenes are colored substances with basic properties. They form colored mono salts with halogen and perhalogen acids. The methene can be liberated from the salt by treatment of the suspension in chloroform, alcohol, or ether with ammonia. Which nitrogen atom in unsymmetrical dipyrrylmethene is more basic is frequently difficult to judge, since the basicity of individual pyrroles is very slight. The compounds form colored complexes with a large number of metal salts such as copper, nickel, zinc, or cobalt acetates as illustrated by the formula below. Picrates, styphnates, picrolonates, flavinates, chloroplatinates,



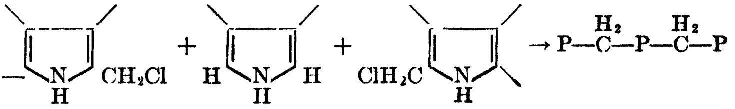
---

[14] SEIDEL, *Z. physiol. Chem.*, **231**, 177, 192 (1935).

and nitrophenolates can also be obtained. Addition compounds with *m*-dinitrobenzene and trinitrotoluene have been isolated.

The behavior of dipyrrylmethenes toward nuclear replacement is, in general, that expected of a pyrrole compound. Nuclear bromination in cold acetic acid occurs when either an alpha or beta position[15] is free. Carboxyl groups in the alpha position can be replaced by bromine in this reaction.[16] At higher temperatures, or in the presence of sunlight, substitution occurs in an α-methyl[17] or ethyl side chain. Silver or potassium acetate in boiling acetic acid or sodium hydroxide in boiling alcohol replaces a nuclear halogen atom by a hydroxyl group. Alcoholic potassium methoxide similarly substitutes methoxyl for bromine.

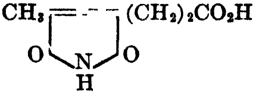
Tripyrryl Compounds.—Two molecules of an α-halogenomethyl-substituted pyrrole will condense with one pyrrole that has both alpha positions free. The product is a tripyrryl system.[18]



P = a pyrryl nucleus.

Tetrapyrryl Compounds.—A chain of four pyrryl nuclei, joined by methylene and methine links, exists in nature as *bilirubin*. This yellow and orange colored material is a biological decomposition product of mammalian blood. It is found in the bile as well as in blood serum. It was isolated first[19] from the gallstones of cattle and subsequently[20] from those of humans. Its empirical composition is $C_{33}H_{36}O_6N_4$. It crystallizes as oblique prisms from dimethylaniline[21] or quinoline and as needles from phenol. Small quantities are purified by successive extractions with ether, alcohol, and chloroform. It has none of the absorption bands that characterize hemin.

Bilirubin has seven active (Zerewitinov test) hydrogen[22] atoms. Energetic oxidation with chromic acid gives hematinic acid.



[15] Fischer and Kirstahler, *Z. physiol. Chem.*, **198**, 44 (1931).

[16] Fischer and Rose, *Ann.*, **519**, 1 (1935).

[17] Fischer and Weichmann, *ibid.*, **492**, 35 (1931).

[18] Fischer and Adler, *Z. physiol. Chem.*, **200**, 209 (1931).

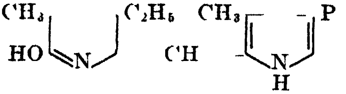
[19] Städeler, *Ann.*, **132**, 325 (1864).

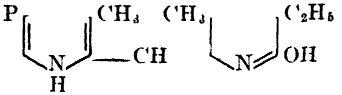
[20] Fischer, *Z. physiol. Chem.*, **73**, 227 (1911).

[21] Fischer and Reindel, *ibid.*, **127**, 303, 314 (1923).

[22] Fischer and Postowsky, *ibid.*, **152**, 309 (1926); Fischer, Plieninger, and Weissbarth, *ibid.*, **268**, 197 (1941).

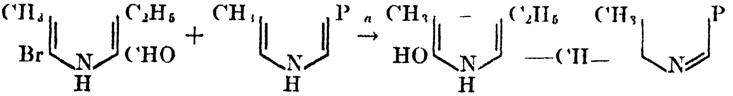
Reduction with hydriodic acid and iodine yields cryptopyrrole and cryptopyrrolecarboxylic acid. Mild reduction with sodium amalgam gives mesobilirubin which splits into neoxanthobilirubic and isoneoxanthobilirubic acids when heated in resorcinol. The constitution


Neoxanthobilirubic acid

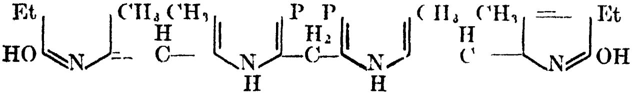

Isoneoxanthobilirubic acid

P = The propionic acid radical, $-CH_2CH_2CO_2H$.

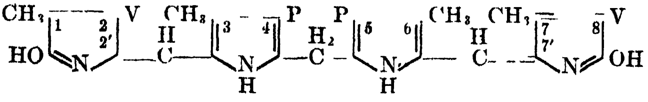
of the first compound is proved by synthesis,[23] that of the second by a resorcinol melt degradation of a synthetic mesobilirubin which has the formula shown below. The structure of bilirubin is also indicated by degradation of the dimethyl ether, when heated in resorcinol, to the methyl ether of vinylneoxanthobilirubic acid, which, in turn, is converted by catalytic hydrogenation to the ether of neoxanthobilirubic acid.


Synthesis of neoxanthobilirubic acid.

[a] HBr joins the two nuclei together, $NaOCH_3$ H_2O at 150° replaces Br by HO.


A synthetic mesobilirubin that gives isoneoxanthobilirubic acid by cleavage.
P = propionic acid.

The structure of bilirubin, therefore, is best represented by

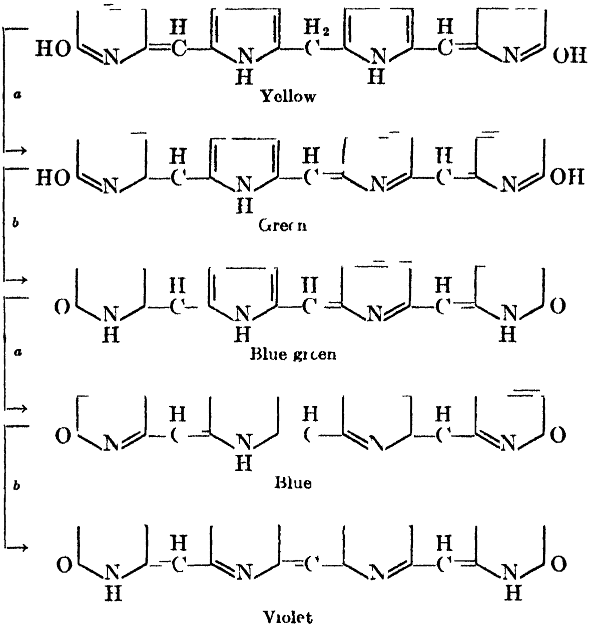

Me = methyl, V = vinyl, P = propionic acid. Note numbering system.

In aqueous or chloroform solution, bilirubin undergoes the Gmelin reaction, a series of color changes produced by nitric acid which contains nitrous acid. The ring at the contact surface changes in succession from green to blue, violet, red, red yellow, and yellow. (See Fig. 4 for possible structural changes).[23] The green and violet colors are especially characteristic. The sensitivity is 1 in 80,000 parts. Alcohol interferes with the test.

---

[23] Seidel and Fischer, *ibid.*, **214**, 145 (1933); Fischer and Haberland, *ibid.*, **232**, 236 (1935).

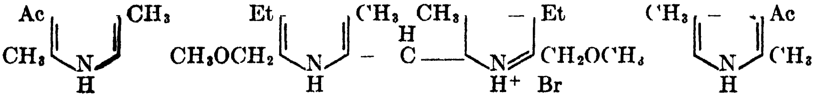
The synthesis of bilirubinoid pigments, which have constitutions similar to bilirubin but without hydroxyl groups, is effected[24] by allowing



[a] Proton removal [b] Isomerization

Fig. 4.—Possible color changes in Gmelin test. Substituents in the beta positions are omitted in these formulas.

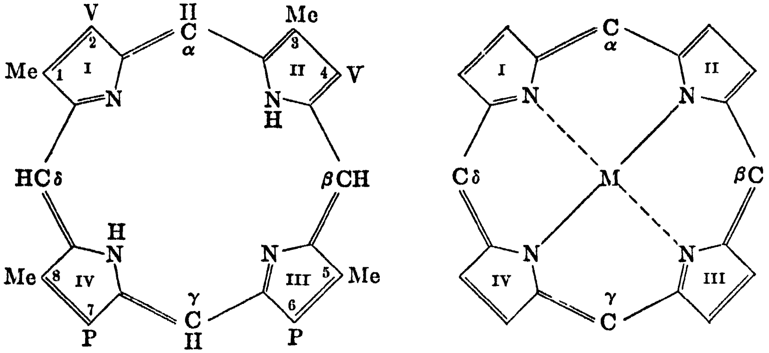
the three molecules shown below to condense to an open chain of four pyrryl nuclei.



Porphyrins.—Four pyrrole nuclei can be linked together in a circular pattern by four carbon atoms so that a great ring of 16 carbon atoms is formed. Alternating single and double bonds occur in the molecule, although it is impossible with our present knowledge to assign them a definite location. The stabilizing influence of resonance appears to be much like that in benzene. The unusual resistance to aerial oxidation, so lacking in the pyrroles, the chemical reactions, so similar to those in benzene, and the general inability to assign a permanent attachment of the two active hydrogen atoms to nitrogen (no isomers are usually obtained either by methylation or by synthesis)[35] support such an opinion. The few cases[25] where isomeric forms are claimed to be present do not detract from the general opinion of a highly resonating and tautomerizing state.

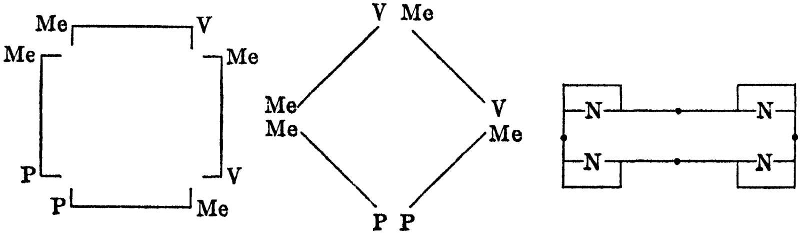
---

[24] FISCHER and KÜRZINGER, *ibid.*, **196**, 213 (1931).



Protoporphyrin IX Porphin metal complex

Me = methyl, Et = ethyl, V = vinyl, P = propionic acid, M = metal.



Abbreviated formula of Fischer

Abbreviated formula of Linstead

Compressed formula sometimes used in this text

FIG. 5.—Structural formulas, abbreviated formulas, and numbering of porphyrins. The substituted porphin is protoporphyrin IX from the blood pigment.

The macro ring formula was first proposed by Küster in 1912. It received experimental support from the exhaustive and painstaking experiments of Hans Fischer[26] and collaborators.

Porphyrins have characteristic spectra that are heavily relied on for detection and identification. They have high melting points and sometimes char without fusing. Picrates and styphnates can be prepared. No optical activity is detected. Magnetic[27] measurements are in agreement with a planar configuration. Metallic compounds are formed either by heating with a metal oxide (*e.g.*, MgO) or salt (*e.g.*, $FeCl_3$). The metal is bound by two primary and two coordinate valencies and is removed by mineral acid.

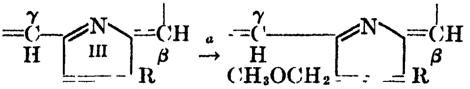
---

[25] ROTHEMUND, *J. Am. Chem. Soc.*, **58**, 625 (1936); **61**, 2912 (1939).

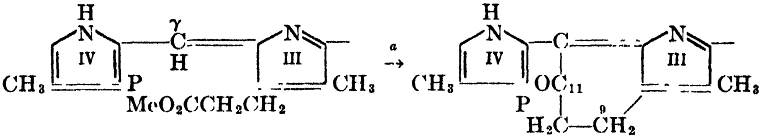
[26] KÜSTER, *Z. physiol. Chem.*, **82**, 463 (1912); **88**, 377 (1913); FISCHER and ORTH, "Die Chemie des Pyrroles," Akademische Verlagsgesellschaft m.b.H., Leipzig, 1937.

[27] PAULING and CORYELL, *Proc. Nat. Acad. Sci.*, **22**, 210 (1936).

The presence of two active hydrogen atoms can be demonstrated[28] by modified Zerewitinov determinations, in a pyridine-xylene mixture (5 to 2 by volume) as a solvent for the porphyrin and in isoamyl ether as a solvent for methylmagnesium iodide. Bromination, nitration, and sulfonation[29] take place. The example of a Friedel-Crafts reaction, shown in the partial formula below, illustrates a very important starting point in the preparation of a propionic acid[30] substituent as will be made clear later. Hydrogen atoms on the γ-methine group have been condensed with other nuclear substituents as in the reaction with mesoetioporphyrin illustrated (partial formula only) below.



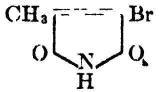
[a] $CH_3OCH_2Cl + SnCl_4$.



Mesoporphyrin dimethyl ester   Mesorhodin

[a] Conc. H_2SO_4. P refers to the methyl propionate radical.

Unlike dyes and other colored substances, porphyrins are not reduced by hydrosulfite or by hydrogen over palladium[31] in aqueous alkali solution, but are affected by hydrogen and platinum in acetic acid.[32] Leuco compounds so obtained are reoxidized by air. Catalytic hydrogenation over Raney nickel at 60° in dioxane converts pyrroporphyrin to mesopyrrochlorin[33] (addition of two hydrogen atoms). Drastic reduction,[34] such as in boiling acetic acid with hydriodic acid and phosphorus iodide, will break the ring. Phylloporphyrin by such treatment yields hemopyrrole, cryptopyrrole, and phyllopyrrole. Stannous chloride[35] also reduces porphyrins to pyrroles.

Vigorous oxidizing agents degrade the ring. Protohemin[36] is converted to hematinic acid; bromorhodoetioporphyrin[37] is broken to bromocitraconimide  by chromic acid. As in all studies of natural products, such reductive and oxidative degradations have supplied important clues to the structural formulas of natural and synthetic porphyrins.

---

[28] Hanrowitz and Zirm, *Ber.*, **62**, 163 (1929); Schmidtz-Dumont and Hamann, *J. prakt. Chem.*, **139**, 162 (1934); Fischer and Goebel, *Ann.*, **522**, 168 (1936).

[29] Fischer and Riedl, *ibid.*, **486**, 178 (1931).

[30] Fischer and Ebersberger, *ibid.*, **509**, 19 (1934).

[31] Conant and Hyde, *J. Am. Chem. Soc.*, **52**, 1233 (1930).

[32] Fischer and Zerweck, *Z. physiol. Chem.*, **137**, 242 (1924); Kuhn and Seyffert, **61**, 2509 (1928).

[33] Fischer and Herrli, *Ann.*, **530**, 230 (1933).

[34] Willstätter and Asakina, *ibid.*, **385**, 188 (1911).

[35] See Fischer and Orth, Ref. 26.

[36] Küster, *Ber.*, **29**, 821 (1896).

[37] Fischer and Treibs, *Ann.*, **466**, 213 (1928).

Naming and Numbering of Porphyrins.—Compounds of this class derive their names from their color, order of discovery, manner of derivation, or other empirical relation. Porphyrin, for example, comes from the Greek word meaning purple; protoporphyrin refers to its position as the first porphyrin from the blood-pigment hemoglobin. The prefix *etio-* originally meant a bleached product but is now applied to all porphyrins derived by decarboxylation of an acid substituent. The prefix *meso-* designates an intermediate reduction state (vinyl to ethyl). If a number of degradation products show very nearly identical spectra, they are given a class name with alphabetical or numerical notations to designate individual members. For example, chlorin is a member of the group of compounds known as "chlorins" because of their green color in ethereal solution. Now that the structures of the porphyrins have been disclosed, it is possible to name them as derivatives of the parent compound porphin. Mesoetioporphyrin then becomes 1,4,5,8-tetramethyl-2,3,6,7-tetraethyl porphin. Iron derivatives have the class name *hem* (for ferrous) or *hemin* (for ferric) attached as a suffix. Protohem and protohemin, for example, are the correct names for the iron-containing porphyrins in human blood, although the prefix *proto-* is frequently omitted. Magnesium-containing complexes are called "phyllins," *e.g.*, porphin phyllin.

If all substituents are alike, no isomers are possible, but if two groups are present in equal amount, four isomeric forms, designated by numbers, can be found. In the case of mesoetioporphyrin, the sequence of groups is shown below.

1 2 3 4
Me Et Me Et

Et Me Et Me
8 7 6 5
Mesoetioporphyrin I
or 1,3,5,7-tetramethyl-
2,4,6,8-tetraethylporphin

1 2 3 4
Me Et Et Me

Me Et Et Me
8 7 6 5
Mesoetioporphyrin II

1 2 3 4
Me Et Me Et

Me Et Et Me
8 7 6 5
Mesoetioporphyrin III

1 2 3 4
Me Me Me Me

Et Et Et Et
8 7 6 5
Mesoetioporphyrin IV

Similarly, coproporphyrin, which is a tetramethyltetrapropionic acid porphyrin found in urea and feces, can exist in four forms depending on the sequence of methyl and propionic groups. In the uroporphyrins, which are found in urea and muscle shells, the groups are acetic and propionic acids. In all these cases, the naming is I, II, III, IV for the isomeric forms depending on whether the sequence is alternate, alternate by pairs, half alternate and half by pairs, or by two groups of fours. It is remarkable that the sequence in nature[38] is always according to I and III with the latter predominating three to one, save in the case of porphyrins from algae.

As the number of groups increases, the possibility of isomers also increases, so that a decision on the form present in any natural product becomes increasingly difficult. The practice in such cases is to convert some of the groups to such substituents as will reduce the number of possible isomers. For instance, decarboxylation will convert a propionic acid group to ethyl, and reduction will convert a vinyl group to ethyl. A portion of the sequence can then be established by comparison with the spectra of a compound of known structure.

Because there is no known method for the conversion of one prophyrin into its isomer without destruction of the great ring, the fact that the sequence of groups in nature is always III or I suggests two natural methods of porphyrin synthesis. Considerable interest attaches, therefore, to the presence of these two forms under various environments and states of health. Cattle,[39] which suffer from animal ochronosis, and the fox squirrel[40] have bones colored with uroporphyrin I.

Isolation and Preparation of Porphyrins.—Porphyrins are obtained from natural sources or by synthesis, The general procedure for isolation of the natural product is to extract the material in question with a mineral acid. The porphyrins so obtained can be purified by the usual process of neutralization, extraction with ether, reextractions with hydrochloric acid, precipitation at definite pH values, accompanied by dialysis and other standard methods.[41]

Synthesis of porphyrins usually starts from dipyrrylmethanes or dipyrromethenes. Preparation[42] of mesoctioporphyrin II illustrates (see Fig. 6) a method for condensing a dicarboxydipyrrylmethane under the influence of acids, preferably formic. Another method of porphyrin synthesis uses brominated dipyrrylmethenes under the dissolving and oxidizing influence of concentrated sulfuric acid, as illustrated for mesoetioporphyrin I,[43] a decarboxylation product of coproporphyrin. This same compound can be prepared from dibromodipyrrlmethenes,[44] but in this case a reducing medium such as boiling formic acid is advantageous. Other organic acids[45] such as tartaric, succinic, citric, and mixtures of these have proved useful as components of melts in which condensation occurs at 190°. Obviously, appropriate mixtures that need no oxidizing or reducing medium can be used. So great, however, is the tendency for the macro ring to form that at the temperature employed (180 to 190°) a considerable number of combinations are possible; and the methenes themselves will serve as the necessary oxidizing or reducing agent if an appropriate medium is absent. Such methods of synthesis often produce a variety of products, particularly if simultaneous decompositions of an acid substituent on the pyrrole nucleus is possible. In the case of phylloporphyrin (page 89), as many as 10 different products are realized.[46] Separation of all forms was accomplished by extraction of

---

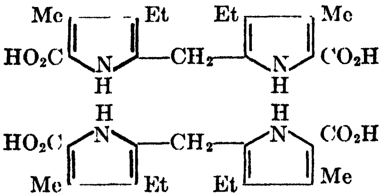
[38] Fischer, *Naturwissenschaften*, **18**, 1026 (1930); Fischer and v. Holt, *Z. physiol. Chem.*, **229**, 93 (1934). See also Ref. 26.

[39] Fink and Fikentscher, *Z. physiol. Chem.*, **202**, 8 (1931).

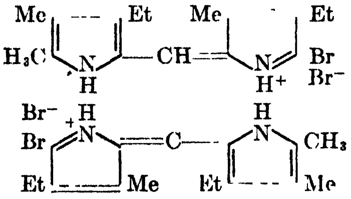
[40] Turner, *J. Biol. Chem.*, **118**, 519 (1937).

[41] Oppenheimer, "Handbuch der Biochemie des Menschau und der Tiere," 2d ed., Vol. I, p. 247, G. Fischer, Jena, 1933. See also Ref. 40.

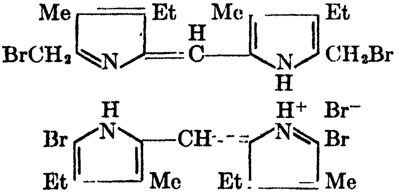
[42] Fischer and Halbig, *Ann.*, **450**, 151 (1926).



Mesoetioporphyrin II from two pyrromethanes by loss of $2CO_2$ and $4H_2O$ with addition of 2H from formic acid.



Mesoetioporphyrin I from two α-methyl-α'-bromopyrromethene hydrobromides by loss of 2HBr and 2H in hot concentrated sulfuric acid which serves as an oxidizing medium.



Mesoetioporphyrin I from an α,α'-dibromomethylpyrromethene hydrobromide and an α,α'-dibromopyrromethene hydrobromide by loss of 4HBr and addition of 2H in a reducing melt such as tartaric, succinic, or citric acid at 0°.

FIG. 6.—Arrangements that illustrate methods for the synthesis of porphyrins.

---

[43] FISCHER and ANDERSAG, *ibid.*, **460**, 201 (1926).

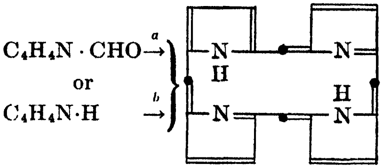
[44] FISCHER and STANGLER, *ibid.*, **459**, 53 (1927).

[45] FISCHER, FRIEDRICH, LAMATSCH, and MORGENROTH, *ibid.*, **466**, 158 (1928); FISCHER and FRÖWIS, *Z. physiol. Chem.*, **195**, 52 (1931); FISCHER and HOLT, *ibid.*, **227**, 139 (1934).

[46] FISCHER and HELBERGER, *Ann.*, **480**, 235 (1930); FISCHER, SIEDEL, and d'ENNEQUIN, *ibid.*, **500**, 137 (1933).

an ethereal solution with different strengths of acid, a process called "acid fractionation."[47]

Porphyrin Compounds.—The parent member of the series is *porphin*. In less than 1 per cent yield, it can be prepared from 2-aldehydopyrrole in boiling formic acid[48] or from pyrrole[49] and formaldehyde in hot pyridine. Use of acet-, propion-, or benz-aldehyde in the latter process produces the corresponding *ms*.-substituted porphyrin.


$C_4H_4N \cdot CHO \xrightarrow{a}$
or
$C_4H_4N{\cdot}H \xrightarrow{b}$
N
H
N
N
H
N

[a] 3 hr. reflux in HCO_2H. [b] 30 hr. at 90 to 95° with H_2CO in pyridine.

Porphin decomposes above 360°. It shows the absorption bands characteristic of the substituted porphyrins. Metallic derivatives are prepared by heating with magnesium oxide, ferric chloride, or copper acetate. The porphin is regenerated with hydrochloric acid.

Two principal sources of substituted porphyrins exist in nature. The first is the blood and other respiratory pigments; the second is from chlorophyll, in which phorbins exist that can be degraded to porphyrins by various chemical methods. In the following sections, groups of compounds indicate a common origin or degradation process.

Protoporphyrins, tetramethyldivinyldipropionic acid-porphins, are of much interest because one of the 15 possible isomers, *viz*., protoporphyrin IX (in Fig. 5) is widely distributed as a respiratory pigment in nature. As a ferrous iron complex and attached to the protein, globin, it becomes hemoglobin[50] present in human blood. With iron in the ferric state, analogous to methemoglobin, but bound to a different protein, it is found in the enzyme, catalase,[51] which converts hydrogen peroxide to oxygen and water. The spectrum of reduced peroxidase,[52] another enzyme, shows the same bands as reduced hemin. The catalytic activity is proportional to the hemin[53] content, though the latter is equivalent to a seventh only of the total iron present. The intercellular respiratory enzyme cytochrome *c* common to animals, bacteria, yeast, and higher plants is probably a methemoglobinlike derivative[54] of protoporphyrin.

---

[47] WILLSTÄTTER and MIEG, *ibid.*, **350**, 1 (1906).

[48] FISCHER and GLEIM, *ibid.*, **521**, 157 (1936).

[49] ROTHEMUND and LONDERGAN, *J. Am. Chem. Soc.*, **58**, 625 (1936).

[50] FISCHER and JORDAN, *Z. physiol. Chem.*, **190**, 75 (1930).

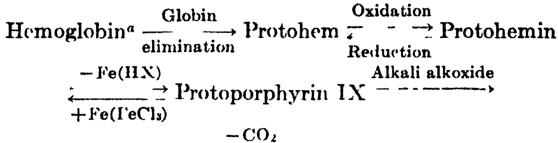
[51] ZEILE and HELLSTRÖM, *ibid.*, **192**, 17 (1930); STERN, *J. Biol. Chem.*, **112**, 661 (1935).

[52] KUHN, HURD, and FLORKIN, *Z. physiol. Chem.*, **201**, 255 (1931).

[53] KEILIN and MANN, *Proc. Roy. Soc. (London)*, **122 B**, 119 (1937).

[54] HILL and KEILIN, *ibid.*, **107 B**, 286 (1930); ZEILE and REUTER, *Z. physiol. Chem.*, **221**, 101 (1933).

Steps in the conversion of hemoglobin to three different porphyrins are shown below. All three of these porphyrins have been synthesized, some by more than one method, so that their structures are known. Protoetioporphyrin, the carboxyl-free product of protoporphyrin, has also been prepared. The sequence of substituents shown below is essentially the same for each porphyrin, since vinyl groups can be reduced and propionic acid groups can be decarboxylated to give ethyl groups. The porphyrins derived from chlorophyll have similar sequences. If the bilirubin chain were closed, the sequence of substituents would be the same as in protoporphyrin IX.



$$\text{Hemoglobin}^{a} \xrightarrow[\text{elimination}]{\text{Globin}} \text{Protohem} \underset{\text{Reduction}}{\overset{\text{Oxidation}}{\rightleftarrows}} \text{Protohemin}$$

$$\underset{+\text{Fe}(\text{FeCl}_3)}{\overset{-\text{Fe}(\text{HX})}{\rightleftarrows}} \text{Protoporphyrin IX} \xrightarrow{\text{Alkali alkoxide}}$$

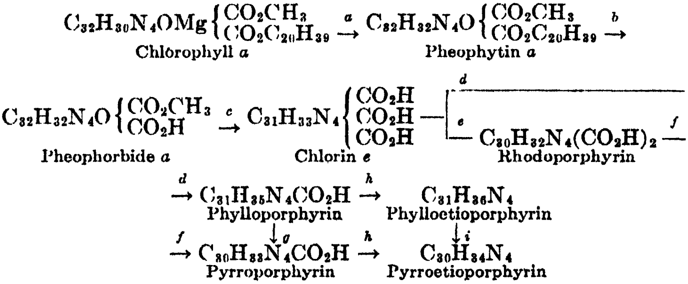
$$\text{Mesoporphyrin IX} \xrightarrow{-\text{CO}_2} \text{Mesoetioporphyrin III}$$

[a] Oxidized hemoglobin ($\text{Fe}^{++} \rightarrow \text{Fe}^{+++}$) is called methemoglobin. Hemoglobin consists of one globin and four protohem molecules or, by weight, 95 percent globin.

FIG. 7.—Degradation of hemoglobin to porphyrins.

	1	2	3	4	5	6	7	8
Protoporphyrin IX	Me	V	Me	V	Me	P	P	Me
Protoetioporphyrin IX	Me	V	Me	V	Me	Et	Et	Me
Mesoporphyrin IX	Me	Et	Me	Et	Me	P	P	Me
Mesoetioporphyrin III	Me	Et	Me	Et	Me	Et	Et	Me

Rhodo-, phyllo-, pyrro-, and pyrroetio-porphyrins are derived by vigorous alkali treatment from chlorophyll *a*, which has been freed of its metal and phytyl group. Steps in the process are shown in Fig. 8.



$$\underset{\text{Chlorophyll } a}{C_{32}H_{30}N_4OMg\left\{\begin{matrix}CO_2CH_3\\CO_2C_{20}H_{39}\end{matrix}\right.} \xrightarrow{a} \underset{\text{Pheophytin } a}{C_{32}H_{32}N_4O\left\{\begin{matrix}CO_2CH_3\\CO_2C_{20}H_{39}\end{matrix}\right.} \xrightarrow{b}$$

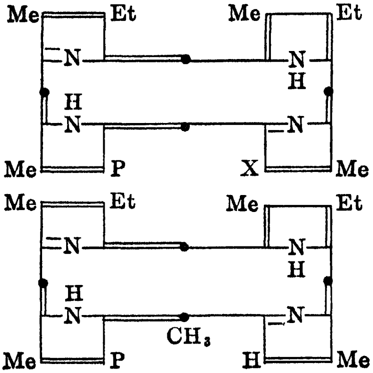
$$\underset{\text{Pheophorbide } a}{C_{32}H_{32}N_4O\left\{\begin{matrix}CO_2CH_3\\CO_2H\end{matrix}\right.} \xrightarrow{c} \underset{\text{Chlorin } e}{C_{31}H_{33}N_4\left\{\begin{matrix}CO_2H\\CO_2H\\CO_2H\end{matrix}\right.} \left[\begin{matrix}\xrightarrow{d}\\ \xrightarrow{e} \underset{\text{Rhodoporphyrin}}{C_{30}H_{32}N_4(CO_2H)_2} \xrightarrow{f}\end{matrix}\right.$$

$$\begin{matrix} \xrightarrow{d} \underset{\text{Phylloporphyrin}}{C_{31}H_{35}N_4CO_2H} & \xrightarrow{h} & \underset{\text{Phylloetioporphyrin}}{C_{31}H_{36}N_4} \\ \downarrow g & & \downarrow i \\ \xrightarrow{f} \underset{\text{Pyrroporphyrin}}{C_{30}H_{33}N_4CO_2H} & \xrightarrow{h} & \underset{\text{Pyrroetioporphyrin}}{C_{30}H_{34}N_4} \end{matrix}$$

[a] Oxalic acid removes the Mg without hydrolysis of the ester. [b] Conc. HCl. [c] Boiled 30 sec. in methyl alcoholic KOH. The chlorin *e* was originally called phytochlorin *e*. [d] Hot alkali or boiling quinoline or phosphoric acid at 140°. [e] Methylalcoholic NaOH at 140 to 190°. Verdoporphyrin is first produced but changes to the stable rhodoporphyrin. [f] Continuation of the vigorous alcoholic caustic treatment. [g] Hot NaOR. [h] Decarboxylation. [i] NaOR. Chlorine is not isolated in the usual preparation of rhodoporphyrins and others in that series but can be assumed to be present as an intermediate step of the more drastic treatment with alkali.

FIG. 8.—Steps in the alkaline degradation of chlorophyll to porphyrin.

Structural formulas, arrived at by degradation and synthesis, are known for all these porphyrins (Fig. 9). To avoid the synthesis of all possible isomers needed for comparison, the sequence of groups was first established[55] by insertion (the steps will be described later) of an ethyl group in the open position of pyrroporphyrin (X = H in Fig. 9) and comparison of the product after decarboxylation with mesoetioporphyrin III. The presence of an unsubstituted position in pyrroporphyrin was originally demonstrated by preparing a bromo derivative and degrading it to bromocitraconimide. As with protoporphyrin, sodium ethoxide converts the vinyl groups present in the 2- and 4-positions in chlorophyll, into ethyl radicals.



Rhodoporphyrin X = COOH
Pyrroporphyrin X = H
Mesoporphyrin IX X = P

Phylloporphyrin.
The methyl group in the γ position suggests that a chain of carbon atoms may have been attached at this point in other related compounds.

Fig. 9.—Structures of the porphyrins derived from chlorophyll *a*.

Phylloporphyrin is the methyl homologue of pyrroporphyrin. Its marked difference in absorption spectra from the other porphyrins and its sensitivity to hydriodic acid suggest substitution on one of the connecting carbon atoms. All four isomers were synthesized[46] in order to establish by comparison the correct structure of the γ-isomer derived from chlorophyll.

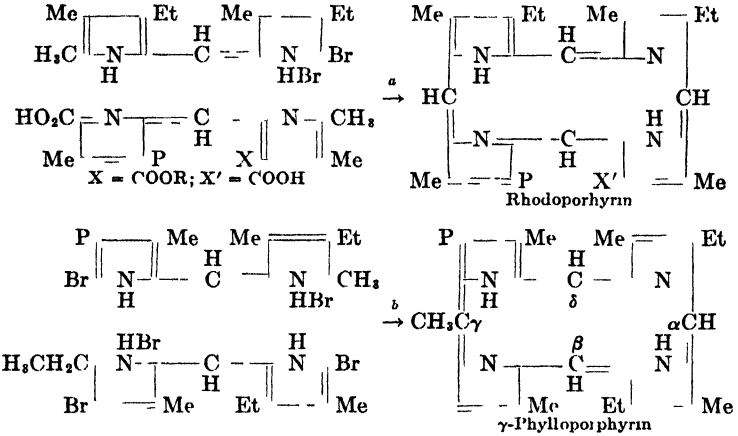
A link[29] between the chlorophyll and hemoglobin series is provided by conversion of pyrroporphyrin to mesoporphyrin by means of the sequence indicated below. Thus a relationship between hemin and

Reagents	Group Produced at C_6
(*a*) $ClCH_2OCH_3 + SnCl_4$	$—CH_2OCH_3$
(*b*) HCl	$—CH_2Cl$
(*c*) $NaCH(CO_2R)_2$	$—CH_2CH(CO_2R)_2$
(*d*) NaOH, HX, heat	$—CH_2CH_2CO_2H$

---

[55] Fischer, Weichmann, and Zeile, *Ann.*, **475**, 248 (1929).

chlorophyll, first suspected in 1851 by Verdeil[56] because iron, accidentally introduced into chlorophyll by use of a crude reagent, produced a hemin-like pigment and then indicated in 1879 by comparison of absorption spectra,[57] was in 1931 defined in exact terms by the brilliant investigation of Hans Fischer.



[a] Condensation followed by hydrolysis. [b] Pyrotartaric acid fusion.

FIG. 10.—Synthesis of rhodoporphyrin XV and γ-phylloporphyrin.

Pheoporphyrin and Phylloerythrin.—Hydriodic acid at 50° converts chlorophyll or pheophorbide into porphyrins (Fig. 13) which are more closely related to the original material than are the products obtained by the brutal alkali treatment.

$$\text{Chlorophyll } a \xrightarrow{\text{HCl}} \text{pheophorbide} \xrightarrow{\text{HI}} \text{pheoporphyrin } a_5 \xrightarrow{\text{HI}} \text{phylloerythrin}$$

Pheoporphyrin has a carboxyl, a carbomethoxy, and a ketone group. Elimination of the carbomethoxy group during the reaction leads to phylloerythrin, the formula of which is indicated by (*a*) its conversion with sodium methoxide to rhodo-, phyllo-, and pyrro-porphyrin; (*b*) its aerial oxidation in methyl alcoholic potash to rhodoporphyrin-γ-carboxylic acid; and (*c*) its reduction by the Wulff-Kizhner process to desoxophylloerythrin, which is also obtained by the action of hydrobromic acid on pheophorbide at 180° in acetic acid. This picture of its structure is completed[58] by the synthesis of desoxophylloerythrin, which in turn can be oxidized with sulfur trioxide and sulfur to phylloerythrin.

---

[56] VERDEIL, *Compt. rend.*, **33**, 689 (1851).

[57] HOPPE-SEYLER, *Z. physiol. Chem.*, **3**, 339 (1879); **4**, 193 (1880).

[58] FISCHER, HECKMAIER, and RIEDMAIR, *Ann.*, **494**, 86 (1932); FISCHER and RIEDMAIR, *ibid.*, **499**, 288 (1932).

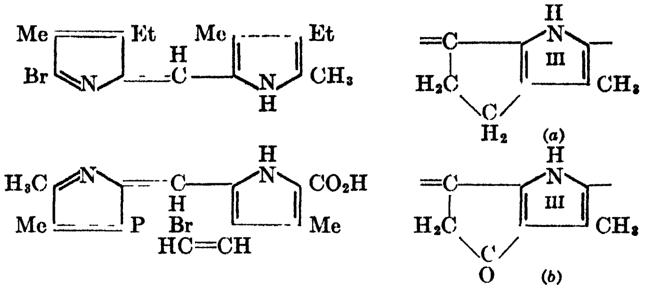
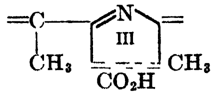


FIG. 11.—Compounds needed for synthesis of desoxophylloerythrin. (b) Partial formula for (a) desoxophylloerythrin, (b) phylloerythrin.

These compounds have an important bearing on the problem of the structure of chlorophyll for they show the presence of a carbocyclic ring. Their isolation is made possible by the gentle action of hydriodic acid, which, under these conditions, is comparable to the biological degradation of chlorophyll to phylloerythrin, which is found in the feces of cows, the bile of sheep,[59] and the bile of oxen.[60]

Chloroporphyrin c_4 is obtained as one of the products from chlorin *e* by gentle reduction with hydriodic acid in acetic acid. Its partial structure[61] is shown below. It can be converted to desoxophylloerythrin by sodium ethoxide. The formula has been established by synthesis.



Deuteroporphyrin is a putrefaction product of blood in which the vinyl group in protoporphyrin is replaced by a hydrogen atom. It forms a dibromo-derivative, which by oxidative degradation yields bromocitraconimide. It is synthesized[62] from a mixture of 4,5-dimethylpyrryl-3,5-dimethyl-pyrrolenmethene hydrobromide and bis (5-bromo-4-methyl-3-propionic acid pyrryl)-methene hydrobromide in succinic acid at 180 to 190°.

Uroporphyrin III is obtained from the urine of patients afflicted with idiopathic porphyrea. The two groups present are acetic acid and propionic acid. Elimination of four molecules of carbon dioxide by 1 per cent hydrochloric acid at 180 to 190° converts the compound to coproporphyrin, which is 1,3,5,8-tetramethylporphin-2,4,6,7-tetrapropionic acid.

---

[59] MARCHLEWSKI, *Z. physiol. Chem.*, **45**, 176 (1905); FISCHER, *ibid.*, **206**, 255 (1932).

[60] LÖBISCH and FISCHLER, *Monatsh.*, **24**, 335 (1903); FISCHER, *Z. physiol. Chem.*, **96**, 293 (1915).

[61] FISCHER, MÜLLER, and LESCHHORN, *Ann.*, **523**, 165 (1935).

[62] FISCHER and KIRSTAHLER, *ibid.*, **466**, 178 (1928).

Porphyrins have been found in bitumen from oil shale.[63] Trinidad oil contains as high as 0.047 of total porphyrin. A bituminous marl from Switzerland contains 0.4 per cent as a vanadium complex. These figures are remarkably high, in view of the fact that the total porphyrin content of dried leaves is 0.8 per cent. Separation is effected by chromatographic adsorption. Identification rests on absorption spectra. Desoxophylloerythrin, mesoporphyrin, mesoetioporphyrin as well as other products have been found. The porphyrins from chlorophyll are more abundant than those from hemin. The discovery of these substances throws an interesting light on the formation of petroleum. Since the carboxylated porphyrins will lose carbon dioxide at 240° in a week, Triebs estimates that the temperature of petroleum formation did not exceed 200°C.

Phorbins.—Chlorophyll,[64] named from the Greek word meaning "green leaf," is considered to be a derivative of the hypothetical phorbin,[65]

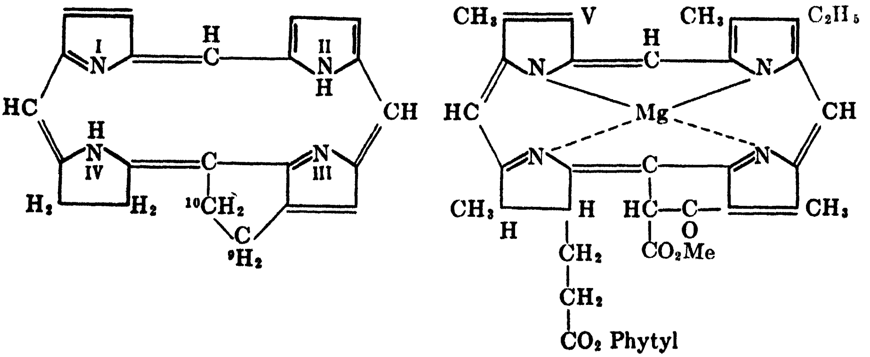


FIG. 12.—Structural formulas for phorbin and for chlorophyll.

which is a dihydroporphyrin with a carbocyclic ring. As isolated by acetone extraction of green leaves, chlorophyll is a dark-green wax consisting of chlorophyll *a*, $C_{55}H_{72}N_4O_5Mg$, and chlorophyll *b*, $C_{55}H_{70}N_4O_6Mg$. In higher plants, the ratio of *a* to *b* is approximately 3:1. In some algae, the *b* form is absent. The bluish-black (bluish green in solution) chlorophyll *a* can be separated from the yellowish-green chlorophyll *b* by extraction of a petroleum ether solution of the mixture with 90 per cent methanol. Chromatographic adsorption on calcium carbonate or on sugar or acid fractionation of the pheophorbides will also separate the two series. The more abundant chlorophyll *a* has received the greater attention. Except for a formyl instead of a methyl group on ring II, the structure of the two compounds is alike.

---

[63] TRIEBS, *ibid.*, **509,** 103 (1934); **510,** 42 (1934); **520,** 144 (1935); TRIEBS and DINELLI, *ibid.*, **517,** 172 (1935); SHEPPARD, *Bull. Am. Assoc. Petroleum Geol.*, **28,** No. 7, 1944.

[64] (*a*) TRIEBS, *Z. angew. Chem.*, **47,** 294 (1934); (*b*) ARMSTRONG, *J. Soc. Chem. Ind.*, **52,** 809 (1923); (*c*) DIETZ, *J. Chem. Education*, **12,** 208 (1925); (*d*) STEELE, *Chem. Rev.*, **20,** 1 (1937); (*e*) FISCHER, *ibid.*, **20,** 41 (1937); (*f*) LINSTEAD, *Ann. Reports*, **34,** 369 (1938).

[65] FISCHER, HERRLE, and KELLERMANN, *ibid.*, **524,** 222 (1936).

The waxlike property of chlorophyll is caused by the presence of the phytyl group $C_{20}H_{39}OH$ or $CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2C(CH_3){=}CHCH_2OH$.

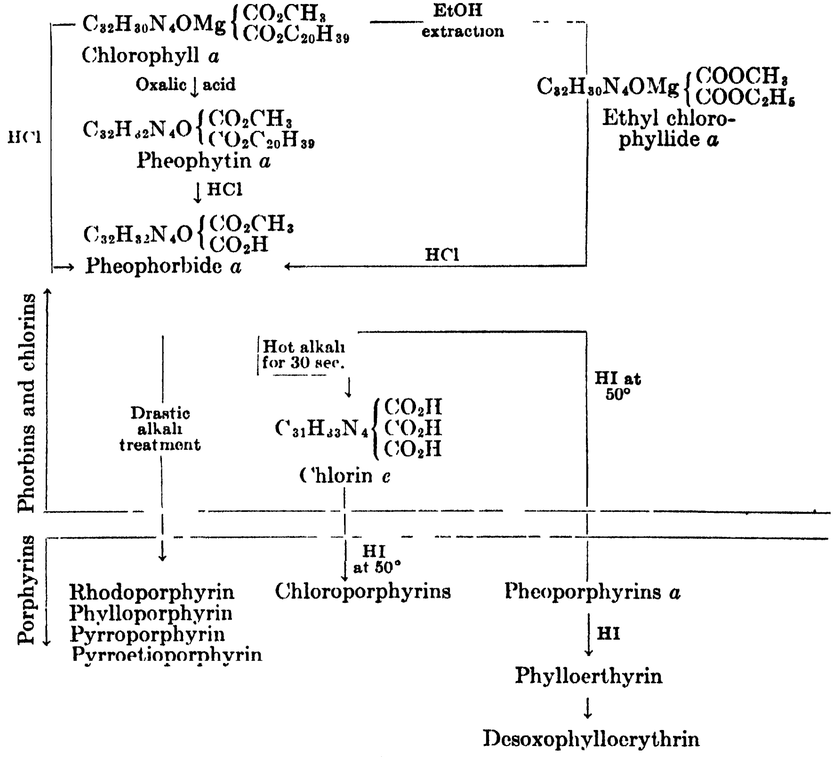


FIG. 13.—Some degradation products of chlorophyll *a*.

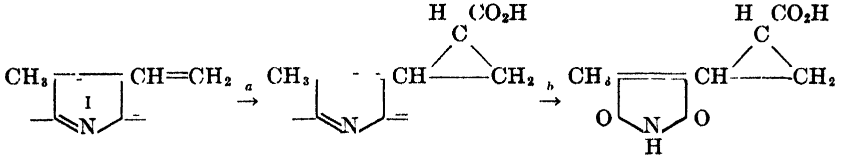
If ethyl alcohol instead of acetone is used as the solvent for extraction, the phytyl group is replaced by ethyl. The position of the phytyl group is determined[66] by pyrolysis of pheophorbide *a*; the carbomethoxy group escapes but the carboxyl group survives. Such stability is characteristic of the propionic acid group, which must therefore support the phytyl radical.

All metal-free derivatives of chlorophyll *a* with the carbocyclic ring intact and the two hydrogen atoms in positions 7 and 8 are known by the class name of phorbides or phorbins.[65] If the ring is opened, they are known as "chlorins" (rhodins in the *b* series). Purpurins are derived from the mild oxidation that takes place in the phase test (oxidation at C_{10}). If the vinyl group is reduced to ethyl, the prefix meso- is attached. Porphyrins of the chlorophyll series do not have extra hydrogen atoms attached to ring IV but may have the carbocyclic ring, in which case they are known as "pheoporphyrins."

---

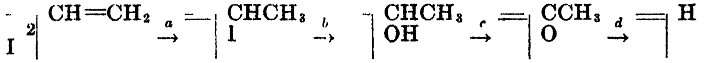
[66] CONANT and HYDE, *J. Am. Chem. Soc.*, **51**, 3668 (1929); CONANT, DIETZ, BAILEY, and KAMMERLIN, *ibid.*, **53**, 2382 (1931); FISCHER, SÜS, and KLEBS, *Ann.*, **490**, 38 (1931).

Many suggestions for the structure of chlorophyll have been made. A recent one by Fischer[64] is shown in Fig. 12. This formula cannot be considered final until confirmed by synthesis, but regardless of that point, this proposal or any other that may supersede it must account for the following facts: (*a*) formation of porphyrins as already described; (*b*) existence of a vinyl group whose presence is revealed by reaction with diazoacetic ester (Fig. 14) and whose location is disclosed[67] by a series of steps (Fig. 15) that lead eventually to another porphyrin, whose structure is known by synthesis; (*c*) formation of a benzoyl derivative, and also an oxime, from chlorophyll and the pheophorbides, suggestive of the presence of a *β*-keto acid system at atoms 9 and 10; (*d*) optical activity[68] present in chlorophyll, pheophytin, pheophorbide, pyrropheophorbide, chlorins, and purpurins and judged to be somewhere in ring IV (Fig. 16); (*e*) a dihydro unit, revealed by electrometric titration[69] as a nitrogen atom of enhanced basicity; (*f*) a series of color changes (green to yellow to green) when chlorophyll, pheophytin, or pheophorbide in ether solution is treated with cold alcoholic alkali whereby oxidative



[a] N_2CHCO_2R. [b] Oxidation.

FIG. 14.—Partial formula that shows the reaction of diazoacetic ester with a vinyl group in compounds of the type of chlorophyll, phorbides, chlorins, purpurins, protohemin and proof of same by oxidative degradation.



[a] HI. [b] H_2O. [c] Spontaneous loss of H. [d] Removal of the acetyl group by heating with conc. HCl.

FIG. 15.—Stepwise conversion of a vinyl to an acetyl group and removal of the latter with hydrochloric acid.

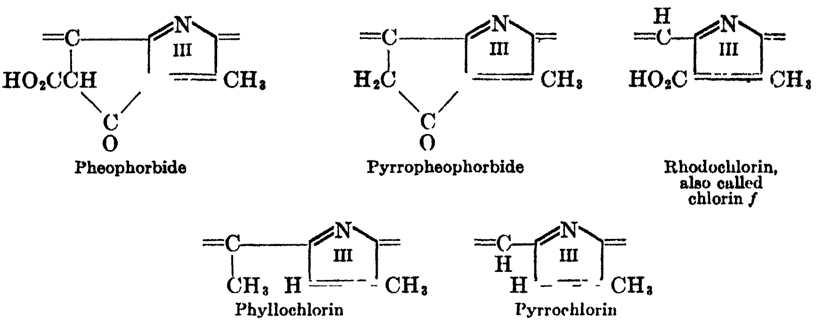
---

[67] FISCHER and BÖCKH, *ibid.*, **516**, 177 (1935); FISCHER and ROSE, *ibid.*, **519**, 1 (1935).

[68] STOLL and WIEDEMANN, *Helv. Chim. Acta*, **17**, 163 (1934); FISCHER, RIEDMAIR, and HASENKAMP, *Ann.*, **508**, 224 (1934).

[69] CONANT, CHOW, and DIETZ, *J. Am. Chem. Soc.*, **56**, 2185 (1934).

hydrolysis occurs and ultimately produces a purple colored product called "pheopurpurin"[70] (Fig. 17); (*g*) the phenomenon of allomerization,[70] *i.e.*, the loss of the ability to crystallize and to undergo the phase test, which occurs when alcoholic solutions of chlorophyll or chlorophyllides are evaporated to dryness and simultaneously absorb oxygen probably at C_{10}.


Pheophorbide

Pyrropheophorbide

Rhodochlorin, also called chlorin *f*

Phyllochlorin

Pyrrochlorin

FIG. 16.—Partial formulas of some optically active degradation products from chlorophyll. The optical activity is in ring IV which has the structure shown in Fig. 12.

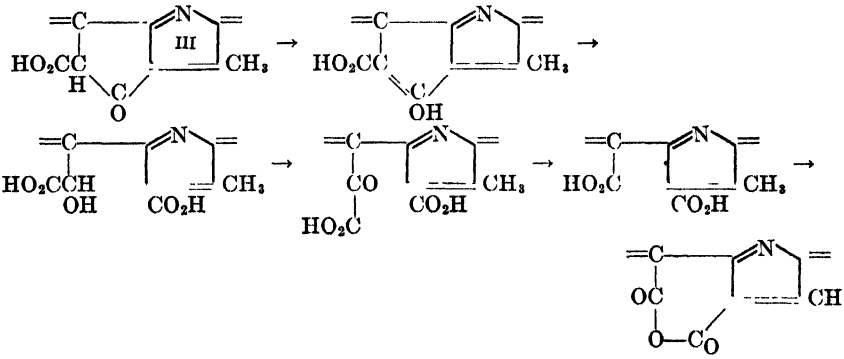


FIG. 17.—Partial formulas that illustrate the changes supposed to occur in the phase test during oxidative hydrolysis of a ring structure that contains a keto carboxylic acid.

Azaporphyrins.—When one or more of the methine groups that join the pyrrole nuclei in porphyrins is replaced by a nitrogen atom, the product is known as an "azaporphyrin." For example, two dibromopyrromethene hydrobromides, treated with ammonia, form a diazaporphyrin.[71] Some monoaza compounds can be formed by similar treatment in alcohol or pyridine solution. The action of phenyl hydrazine at 160 to 200° on the autoxidation product of 2,5-dimethyl-2-ethylpyrrole-5-ethylurethane also leads to a diazaporphyrin.[72].

---

[70] CONANT, KAMMERLING, and STEELE, *ibid.*, **53**, 1615 (1931); STEELE, *ibid.*, **53**, 3171, (1931).

[71] FISCHER, HABERLAND, and MÜLLER, *Ann.*, **521**, 122 (1936); FISCHER and MÜLLER, *ibid.*, **528**, 1 (1937).

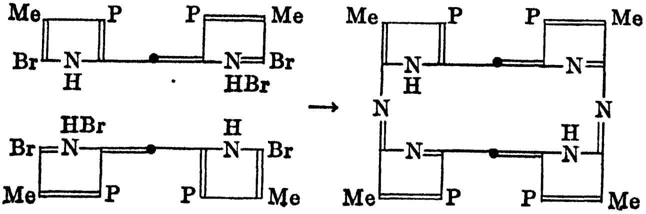
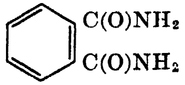


FIG. 18.—Units for formation of diazacoproporphyrin II.

Phthalocyanines.—In the industrial preparation of phthalimide by passage of ammonia into molten phthalic anhydride in iron vessels, traces of a dark blue substance are often found in the molten imide. The insolubility in the usual aqueous and organic solvents enables an easy separation of this stable crystalline iron-containing compound from the imide. Hot nitric acid, aqua regia, or cold potassium permanganate decomposes it to phthalimide and a ferric salt; concentrated sulfuric acid at 100° changes it to phthalic acid, phthalimide, ammonium sulfate, or ferrous sulfate; and distillation with soda lime converts it to benzonitrile and ammonia. A carbon and hydrogen analysis shows an atomic ratio of 4 carbon to 1 nitrogen. Hence, two nitrogen atoms are present with every phthalic acid residue. Such results suggest that these phthalocyanines are derived from dehydration products of phthalamide.



A blue magnesium phthalocyanine[73] is obtained from *o*-cyanobenzamide $NC{\cdot}C_6H_4{\cdot}C(O)NH_2$ and magnesium oxide at 240 to 250° in the presence of naphthalene as a diluent. Phthalonitrile,[74] *o*-$C_6H_4(CN)_2$, readily forms similar blue products when heated with magnesium oxide, cuprous chloride, and similar compounds. Molecular-weight determinations in boiling naphthalene indicate four units in the molecule. The most reasonable conclusion compatible with these facts is that the phthalocyanines consist of four isoindole rings with extracyclic nitrogen atoms. X-ray measurements[75] confirm the tetrazoporphyrin structure.

The preparation from phthalimide consists in a treatment with concentrated ammonia to obtain the phthalamide, followed by dehydration

[72] FISCHER, *ibid.*, **527**, 1 (1936).

[73] LINSTEAD, *J. Chem. Soc.*, 1016 (1934); BYRNE and LINSTEAD and LOWE, *ibid.*, 1017 (1934).

[74] LINSTEAD and LOWE, *ibid.*, 1022 (1934); DENT and LINSTEAD, *ibid.*, 1027; BARRETT, DENT, and LINSTEAD, *ibid.*, 1719 (1936).

[75] LINSTEAD and ROBERTSON, *ibid.*, 1736 (1936).

with hot acetic anhydride to obtain cyanobenzamide and then treatment at 240 to 260° in naphthalene with magnesium oxide, antimony, iron, ferric oxide, ferrous sulfide, nickel, nickel oxide, cobalt oxide, or many other metals and oxides. When phthalonitrile, made by prolonged boiling of phthalamide with acetic anhydride, is heated with magnesium or copper, the blue magnesium or copper phthalocyanine is formed. Phthalimide[73] itself will form the large ring compound when heated with metallic magnesium in a stream of ammonia.

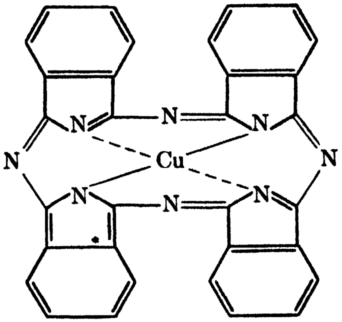


FIG. 19.—Formula for the copper phthalocyanine.

The bright blue copper phthalocyanine is one of the most stable compounds in the series. It is unaffected by molten potassium hydroxide, by boiling hydrochloric acid, or by solutions in concentrated sulfuric acid. It can be sublimed at about 580° under low pressure in an inert atmosphere.

Conversion from the metallic salt to the free phthalocyanine is accomplished by sifting the solid material into concentrated sulfuric acid at about −3° with stirring. After filtration, the metal-free compound is precipitated by pouring on ice. Some decomposition to phthalimide occurs during the process. The free phthalocyanine may also be prepared by the action of sodium or potassium amylate in an amyl alcohol solution of phthalonitrile at 140°.

The greenish-blue phthalocyanine dissolves in cold concentrated sulfuric acid, from which it can be recovered unchanged. By hydrolysis in hot sulfuric or nitric acid, half the nitrogen appears as an ammonium salt and the remainder as phthalimide. It can be heated in a soda-lime glass tube until the glass softens with slight decomposition only to benzonitrile. The benzene ring can be halogenated or made to undergo other conventional reactions.

Problems

1. Give the products obtained from the following: (*a*) 2,4-Dimethylpyrrole in acetic acid, treated with bromine.[76] (*b*) Hemopyrrole (2 g.) in 5 cc. of alcohol and

---

[76] FISCHER and SCHEYER, *Ann.*, **434**, 237 (193).

1.1 cc. of 40 per cent formaldehyde solution, treated with 5 drops of concentrated hydrochloric acid.[6] (*c*) 2,4-Dimethyl-3-aldehydopyrrole, heated in an alcoholic formalin solution.[3a] (*d*) 2,4-Dimethyl-3-acetylpyrrole with glyoxal.[77] (*e*) Cryptopyrrylmagnesium halide with butyryl chloride.[14] (*f*) Furfural and cryptopyrrole in acetic acid with a trace of hydrobromic acid.[78] (*g*) Thiophene-α-aldehyde and cryptopyrrole in alcohol solution with a few drops of hydrobromic acid.[79] (*h*) A solution of bromine in acetic acid added slowly with trituration to a solution of 2,4-dimethyl-3-propylpyrrole in acetic acid, so as to obtain the maximum effect of bromine.[79] (*i*) 2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole in dry ether, heated on a water bath, with 4 moles of sulfuryl chloride.[12] (*j*) Sulfuryl chloride (2 moles) in anhydrous ether added, with stirring, to a dry ethereal solution of 2,4-dimethyl-3-carbethoxypyrrole.[80]

2. Formulate the reaction for 3,5,3′,5′-tetramethyldipyrryl ketone, heated for 2 hr. at 100 to 110° in a sealed tube with a solution of phosgene in toluene.[8a]

3. Give the products obtained under the following conditions: (*a*) 2,5-Dimethyl-3-aldehydopyrrole and 2,4-dimethyl-3-carbethoxypyrrole with concentrated hydrochloric acid.[81] (*b*) 2,5-Dimethyl-3-aldehydopyrrole with 2,4-dimethyl-3-carbethoxypyrrole in concentrated hydrochloric acid.[81] (*c*) 2,3-Dimethyl-4-carbethoxy-5-aldehydopyrrole with 2,5-dimethyl-4-carbethoxypyrrole and concentrated hydrochlorid acid.[79] (*d*) 3,4-Dimethyl-5-carbethoxy-2-aldehydopyrrole with 2,3,4-trimethylpyrrole in acetic acid with a few drops of hydrobromic acid.[82] (*e*) 2,4-Dimethyl-3-cyano-5-carbethoxypyrrole with formic acid in the presence of hydrobromic acid.[83] (*f*) 3-Amino-2,4-dimethyl-5-carboxypyrrole with formic acid in the presence of hydrobromic acid.[84] (*g*) 2-Methyl-5-carbethoxy-3-(β-propionic acid)-pyrrole heated with formic acid in a water bath.[85]

4. The following syntheses are carried out to obtain intermediates for the syntheses of porphyrins. Name the products of the reaction of (*a*) 3,4′,5′-Trimethyl-3′-ethyl-4-carbethoxydipyrrylmethane hydrobromide with bromine in solution in acetic acid.[17] (*b*) 3,3′-Dimethyl-4,4′-dipropyl-5,5′-dicarboxydipyrrylmethane with bromine in solution in formic acid.[86] (*c*) 3′-Bromo-4,4′,5-trimethyl-3-ethyl-5′-carboxydipyrrylmethene with bromine in solution in formic acid.[67] (*d*) 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethane with ferric chloride.[87] (*e*) Bis (3-propionic acid-4-methyl-5-carbethoxypyrryl)-methane dissolved in acetic acid and treated with concentrated ferric chloride solution on a water bath at 60°.[7]

5. State the products obtained from the reaction of 5,5′-Dibromo-3,3′-dimethyl-4,4′-diethylpyrrylmethene hydrobromide heated at 195° in the presence of succinic acid with 4,3′-dimethyl-5,5′-di(bromomethyl)-3,4′-diethyldipyrrylmethene hydrobromide.[44]

6. What is the product of the following reactions? (*a*) 1-Hydroxyl-2,5-dimethyl-3,4-dicarbethoxypyrrole heated with formic acid with addition of some perchloric acid.[88] (*b*) 2,4-Dimethyl-3-cyano-5-carboxypyrrole[89] or 3-amino-2,4-dimethyl-5-carboxypyrrole[90] treated with formic acid in the presence of hydrobromic acid. The empirical compositions of the three products obtained in this example are respectively $C_{13}H_{17}N_2O_6Cl$, $C_{15}H_{15}N_4Br$, and $C_{18}H_{21}N_4Br_3$.

---

[77] FISCHER and EISMAYER, *Ber.*, **47**, 2019 (1914).

[78] FISCHER and NENITZESCU, *Z. physiol. Chem.*, **145**, 303 (1925).

[79] FISCHER and SCHORMÜLLER, *Ann.*, **482**, 232 (1930); FISCHER, GOLDSCHMIDT, and NÜSSLER, *ibid.*, **486**, 1 (1931); FISCHER and BELLER, *ibid.*, **444**, 238 (1935).

[80] FISCHER, STURM, and FRIEDRICH, *ibid.*, **461**, 267 (1928).

[81] PILOTY, KRANNICH, and WILL, *Ber.*, **47**, 2531 (1914).

[82] FISCHER and HIERNEIS, *Ann.*, **492**, 31 (1931).

[83] FISCHER and ROTHEMUND, *Ber.*, **63**, 2252 (1930).

[84] FISCHER and ZEILE, *Ann.*, **483**, 262 (1930).

[85] FISCHER and HUSSONG, *ibid.*, **492**, 148 (1932).

[86] FISCHER, GOLDSCHMIDT, and NÜSSLER, *ibid.*, **486**, 40 (1931).

[87] PILOTY, KRANNISCH, and WILL, *Ber.*, **47**, 2531 (1914).

7. The presence of a vinyl group in mesoetioporphyrin and in chlorophyll can be demonstrated by the use of diazoacetic ester. How would you prove that the vinyl group had been attached to a pyrrole nucleus instead of to one of the methene carbon atoms?[91]

8. $\alpha,\beta,\gamma,\delta$-Octamethylporphinogen might form by heating pyrrole, acetone, and hydrochloric acid on a water bath. Write the formula for the proposed compound.[92]

9. Pyrroporphyrin, derived from chlorophyll, differs from mesoporphyrin derived from hemin by the presence of a hydrogen atom instead of a propionic acid group in position 6. How would you convert mesoporphyrin to pyrroporphyrin? Compare your proposal with the one actually used.[30] How would you convert pyrro- to meso-porphyrin[29] and deutero- to proto-porphyrin?[90]

10. Devise a synthesis for pyrroetioporphyrin (1,3,5,8-tetramethyl-2,4,7-triethylporphyrin)[93]; for coproporphyrin I and II[43]; for rhodoporphyrin [93]

11. How would you prepare a 5,5′-dibromopyrromethene hydrobromide from a pyrrole compound? What is the product of its reaction with ammonia?[71] (Use 3-methylpyrrole-4-propionic acid as the pyrrole compound from which this series starts.)

12. Give the products of the reaction of the following: (*a*) *o*-Cyanobenzamide (40 g.) heated for 1 hr. at 260° with 10 g. of metallic antimony in 20 g. of naphthalene.[73] (*b*) Phthalonitrile (4 mole) heated at 150 to 180° with 2 moles of dry cuprous chloride.[74] (*c*) Phthalonitrile heated to 150 to 195° with cupric acetate.[74] (*d*) Phthalonitrile refluxed with anhydrous zinc chloride.[74]

13. What product is possible when a solution of cryptopyrrole is refluxed with acetone mesityl oxide or phorone in the presence of hydrochloric acid?[94]

14. What is the product obtained from heating the following? (*a*) One gram of 5-hydroxy-2(chloromethyl)-4-methyl-3-carbethoxypyrrole dissolved in benzene on a water bath for 2 hr. with 0.5 g. of opsopyrrole.[18] (*b*) 3,3′Dimethyl-5,5′-di(methoxymethyl)-4,4′-diethyldipyrrylmethene with 2,4-dimethyl-3-acetylpyrrole in benzene solution on a water bath.[24]

15. Write the equations for the reactions that result when cryptopyrrole is treated with ethylmagnesium bromide and the product of this step is allowed to stand overnight with a solution of phosgene in toluene.[8]

---

[88] Fischer and Smeykal, *ibid.*, **57**, 544 (1924).

[89] Fischer and Rothemund, *ibid.*, **63**, 2252 (1930).

[90] Fischer and Zeile, *Ann.*, **483**, 262 (1930); **468**, 98 (1929).

[91] Fischer and Medick, *ibid.*, **517**, 246 (1935). See also Ref. 64*e*.

[92] Fischer, Halbig, and Walach, *ibid.*, **452**, 273 (1927).

[93] Fischer, Berg, and Schormüller, *Ann.*, **480**, 109 (1930); Fischer, Kirstahler, and Zychlinski, *ibid.*, **500**, 1 (1932).

[94] Fischer, Schormüller, and Windecker, *ibid.*, **498**, 284 (1932).

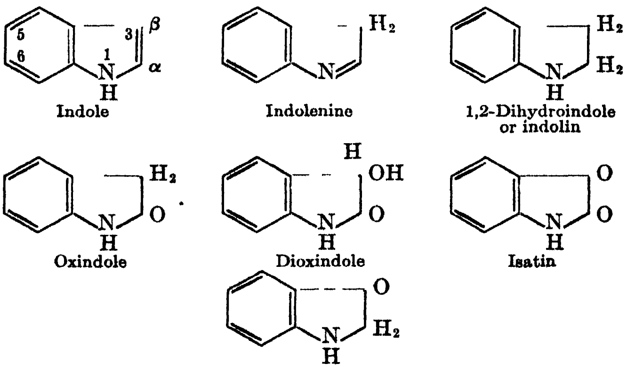
CHAPTER VI

CONDENSED PYRROLE SYSTEM

INDOLES

By 1866, two derivatives only of indigo blue were known; one was indigo white, and the other isatin. In a study of the constitution of indigo, Baeyer elected to reduce isatin, the more stable of the two derivatives, with sodium amalgam in alkaline solution and obtained dioxindole. By reducing in acid solution with tin and hydrochloric acid or with sodium amalgam, he removed one of the oxygens and obtained oxindole.[1] Both compounds were named as derivatives of indole, the then unknown hypothetical parent of the indigo compounds. Later, in the same year, he removed the last oxygen by heating with zinc dust and thus obtained indole.[2] Historically, this last reaction has the added interest that it was the first time a zinc-dust pyrolytic degradation was made.

Although indigo has contributed its name to the series and furnished an early incentive for study, it is by no means the sole important compound. Members of this group are widely distributed in nature as alkaloids, products of putrefaction, and dyes. The study of these compounds has greatly enriched organic chemistry.



Indole

Indolenine

1,2-Dihydroindole
or indolin

Oxindole

Dioxindole

Isatin

Indoxyl

FIG. 1.—Naming and numbering of indole compounds.

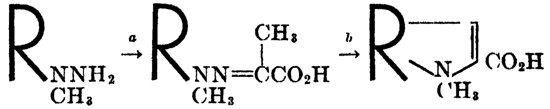
Methods of Synthesis.—In 1883, Fischer[3] was studying the properties of the phenylhydrazone of pyruvic acid and found the remarkable behavior with acids, which in the succeeding years has become one of the outstanding methods for the synthesis of indoles and is known as the *Fischer indole synthesis* (see below). The elimination of ammonia[4] from the phenylhydrazone occurs under the influence of alcoholic hydrochloric acid, sulfuric acid, cupric chloride, cupric bromide, platinous chloride, or better, zinc chloride. The action of zinc chloride is catalytic; not more than 1 per cent is necessary. Condensation can occur even at room temperature, although heat is usually necessary.

---

[1] BAEYER and KNOP, *Ann.*, **140**, 9 (1886).

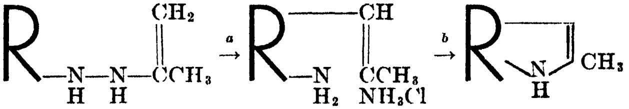
[2] BAEYER, *ibid.*, **140**, 295 (1886); *Suppl. Bd.*, **7**, 56 (1870).

[3] FISCHER and JOURDAN, *Ber.*, **16**, 2241 (1883); FISCHER and HESS, *ibid.*, **17**, 559 (1884); *Ann.*, **236**, 126 (1886).



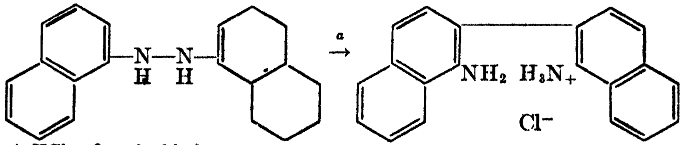
[a] Condensation of the hydrazine with pyruvic acid. [b] HCl or $ZnCl_2$.

Robinson[5] explains the changes by assuming an enolization—a ketimine to enimine change—followed by an *o*-benzidine rearrangement with elimination of ammonium chloride (see below).



[a] The enimine form of the hydrazone acts as a hydrazo compound and rearranges. [b] Elimination of NH_4Cl.

His proposal is in agreement with (*a*) the relatively mild agent necessary for indole formation in the case of readily enolizable hydrazones, such as the phenylhydrazone of phenylacetaldehyde, which forms an acetyl derivative with boiling acetic anhydride, and the hydrazones of aldehydes or ketones with negative groups in the beta position to the carbonyl, as contrasted with the more vigorous treatment (zinc chloride at 180°) needed for the preparation of an indole from the phenylhydrazone of acetophenone; (*b*) the similarity that the process has to the known *o*-benzidine rearrangement of *α*-hydrazonaphthalene, which is an intermediate step in the preparation of the dibenzcarbazole as shown below; and (*c*) the successful application of the principle to a new synthesis of tetraphenyl and tetraanisylpyrrole in excellent yield.[6]



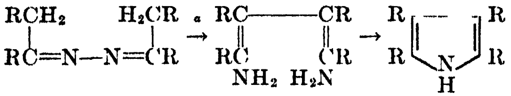
[a] $SnCl_2 + HCl$. One double bond only is pictured in order to illustrate better the similarity to the proposed mechanism.

---

[4] Fischer, *Ber.*, **19**, 1563 (1886); Nef, *Ann.*, **266**, 72 (1891); Arbuzov and Tichvinskii, *J. Russ. Phys. Chem. Soc.*, **45**, 69, 694 (1913).

[5] Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918).

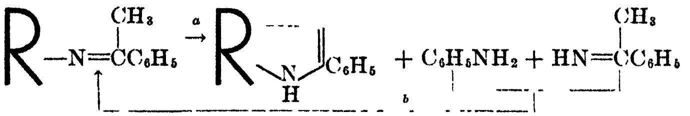
[6] King and Paterson, *ibid.*, 44 (1936); *cf.* Ref. 5.



R = phenyl or anisyl.

[a] Phenylbenzylketazine, previously prepared from desoxybenzoin and hydrazine hydrate, is treated with dry HCl at 180°.

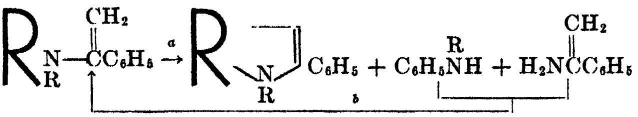
Reddelien[7] offers another explanation, based on his observation that acetophenone anil is oxidized to 2-phenylindole by phenylhydrazine or phenylhydrazones (see Fig. 2). The products from the simultaneous reduction of the hydrazone to aniline and an imine combine to form an anil so that the process, once the initial step has been induced to occur, generates its own necessary intermediate and proceeds to completion. An adaptation of this mechanism to the case of N-substituted phenylhydrazones is shown below.



[a] Phenylhydrazine will oxidize the anil to indole and undergo reduction to aniline and ammonia. An intermediate indolenine stage, $C_6H_4\left\{\begin{matrix}CH_2\\N{=}\end{matrix}\right\}CC_6H_5$, is a likely intermediate that rearranges to the stable indole.

[b] The anil is regenerated by elimination of ammonia.

FIG. 2.—Fischer's indole synthesis according to the intermediate anil mechanism of Reddelien.



Small R = alkyl group.

[a] Oxidation of the amine by the hydrazone. [b] Condensation of the two amines by loss of NH_3 to form the starting material.

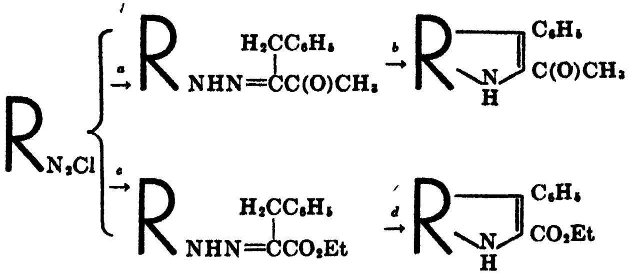
The Japp-Klingemann synthesis[8] provides a novel and valuable way to obtain the necessary hydrazone. Phenyldiazonium chloride and the sodium salt of a keto acid yield a phenylhydrazone with extrusion of the carboxyl group. If the carboxyl group is protected by esterification, the acetyl group is lost. These possibilities are illustrated below by the production of 2-acetyl-3-phenylindole or of ethyl 3-phenylindole-2-carboxylate, depending on whether the sodium carboxyl or the acetyl group is eliminated.[9]

---

[7] REDDELIEN, *Ann.*, **388**, 179 (1912).

[8] JAPP and KLINGEMANN, *Ber.*, **21**, 549 (1888).

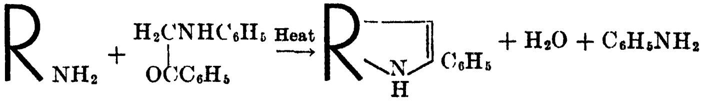
[9] MANSKE, PERKIN, JR., and ROBINSON, *J. Chem. Soc.*, 1 (1927).



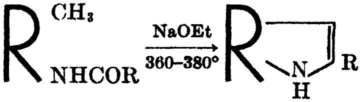
[a] $Na[C(COCH_3)(CH_2C_6H_5)(CO_2Na)]$. Extrusion of the carboxyl group. [b] HCl aq. [c] $Na[C(COCH_3)(CH_2C_6H_5)(CO_2Et)]$. Extrusion of the acetyl group. [d] Alc. HCl.

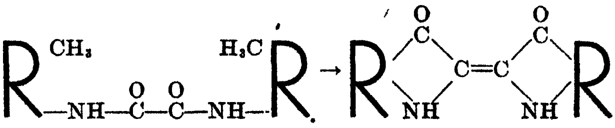
A second general method of synthesis uses the reaction of arylamines with α-halogenated ketones.[10] A phenacylaniline, isolable at low temperatures, but usually not separated, is the first product. A second molecule of the aniline completes the reaction. Compounds such as α,β-dichloroethyl ether,[11] which dissociates to chloroacetaldehyde during the reaction, are suitable agents also in place of the ketone.

$$C_6H_5NH_2 + BrCH_2C(O)C_6H_5 \rightarrow C_6H_5NHCH_2C(O)C_6H_5$$



A third method for the preparation of indoles consists of an intramolecular Claissen condensation of an acyl or aroyl derivative of an *o*-toluidine. This useful reaction, known as Madelung's,[12] gives good results with the acetyl and benzoyl derivatives, but not with the formyl. The oxalyl derivative, employed in this way, was the basis for a novel synthesis of indigo (see page 132).





Reagent sequence: hot $NaOC_5H_{11}$, HNO_3, $Na_2S_2O_4$, $FeCl_3$, hydrolysis of the diimine.

---

[10] Möhlau, *Ber.*, **15**, 2480 (1882); Bischler, *ibid.*, **25**, 2860 (1892); Bischler and Fireman, *ibid.*, **26**, 1336 (1893).

[11] Berlinerblau, *Monatsh.*, **8**, 180 (1887); Berlinerblau and Polikiev, *ibid.*, **8**, 187 (1887); Wolff, *Ber.*, **20**, 427 (1887); **21**, 123, 3360 (1888).

[12] Madelung, *Ber.*, **45**, 1128 (1912); Verley, *Bull. soc. chim.* [4], **35**, 1039 (1924); Salway, *J. Chem. Soc.*, **103**, 351 (1913).

The common procedure for the synthesis of indigo is available also as a method for the synthesis of indoles[13] (see page 122). Some other methods[14] that have been used are (*a*) pyrolysis of N-methyl-*o*-toluidine with nickel at 300 to 330°; (*b*) nitration of phenylacetone, reduction of the product, and then dehydration; (*c*) condensation of *o*-nitrotoluene with ethyl oxalate, reduction of the *o*-nitrophenylpyruvic acid product followed by decarboxylation.

Reactions of Indole.—In general, the reactions of indole are similar to those of pyrrole, modified by the presence of a benz nucleus. One important difference, however, is that the reaction of indolylmagnesium bromide (from indole and ethylmagnesium bromide) with alkyl halides yields largely a 3-alkylindole[15] instead of a 2-derivative. This difference is either the result of activation of the C_3 position by the adjacent benz ring, as in naphthalene, or the result of a shortened ketimine-enimine system as discussed on page 62. Both factors may operate.

The reaction with sodium alkoxide at high temperatures, whereby alkyl groups are introduced, occurs with α-methylindole only, not with indole or 3-methylindole.[16] Amyl nitrite[17] gives β-isonitrosoindole derivatives. If the beta position is already occupied by a substituent, amorphous products form. Chlorine and bromine react violently and form tars. The reaction is moderated by an N-benzoyl group. 3-Chloro- or 3-bromo-N-benzoylindole results.[18] Dilute ammonia or alcoholic sodium ethoxide then removes the benzoyl group. A molecule of sulfuryl chloride introduces a chlorine atom into indole at C_2 or C_3; two molecules yield the 2,3-dichloroindole.[19] Iodine acts less vigorously than the other halogens and forms 3-iodoindole[20] in cold dilute alkaline solution. A methyl group at C_2 does not interfere with this reaction, but one at C_3 does. Some oxidation to indigo simultaneously occurs.

The above reactions show the influence of an imino system which, phenol-like, makes substitution on the nucleus easier or, enol- and keto-like, undergoes ketimization to the indolenine or ammono aldehyde form. Hence the Kolbe synthesis (chloroform and alkali) yields β-aldehydoindole,[21] together with much 3-chloroquinoline by ring expansion, the prevailing reaction with pyrroles; the acyl group of N-acylindole (from an N-sodium salt and acyl halide) undergoes thermal rearrangement to the 3-position, a reaction for which the phenolic parallel is the Fries rearrangement; bisulfite forms a crystalline addition compound in which the ketimine form serves as an aldehyde; and aldehydes or compounds that contain an active carbonyl group condense with the active methylene group at C_3.

---

[13] VORLÄNDER and APELT, *Ber.*, **37**, 1134 (1904).

[14] CARRASCO and PADOA, *Gazz. chim. ital.*, **36**, II, 512 (1906); BAEYER and JACKSON, *Ber.*, **13**, 187 (1880); POLYAKOVA, *Masloboino Zhirovoe Delo*, **11**, 452 (1935); *C.A.*, **30**, 4869 (1936).

[15] ODDO, *Gazz. chim. ital.*, **63**, 315 (1934).

[16] ODDO and ALBERTI, *ibid.*, **63**, 236 (1933); *C.A.*, **27**, 3933 (1933).

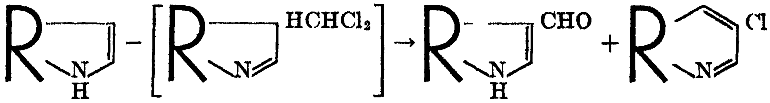
[17] AJELLO, *Gazz. chim. ital.*, **69**, 460 (1939).

[18] WEISSGERBER, KLEMM, HERZ, and KRAFT, *Ber.*, **46**, 651 (1913).

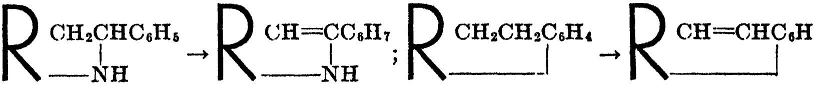
[19] MAZZARA and BORGO, *Gazz. chim. ital.*, **35**, II, 563 (1905).

[20] PAULY and GUNDERMANN, *Ber.*, **41**, 3999 (1908).

[21] ELLINGER, *ibid.*, **39**, 2515 (1906).



Addition of hydrogen at the 2,3-bond of indole occurs readily by an electrolytic method at a lead cathode in aqueous alcoholic sulfuric acid.[22] At 200° over nickel, indole is hydrogenated to 2-ethylcyclohexylamine;[23a] at room temperature over platinum, it is reduced to dihydro- and octahydro-indole;[23b] at 170 to 190° over copper chromite catalyst, it is converted to 2,3-dihydroindole; and at 250° over Raney nickel, it is reduced to octahydroindole.[24] Introduction of a phenyl substituent in the 2-position of indole causes the selective hydrogenation over copper chromite at the 2,3-position in indole to take place at 155°, conditions almost as mild as those required for a simple olefin bond or for the 9,10-position in phenanthrene. Over copper chromite, the phenyl group of 2-phenylindole is hydrogenated at 190°, a temperature so low as to warrant the assumption[24] that the hydrogens in the 2,3-dihydro product move to a position in the aromatic nucleus, in much the same way as the hydrogens in 9,10-dihydrophenanthrene migrate to the benz nucleus so that tetrahydro- or sym-octahydro-phenanthrene is eventually formed. The two hydrogens in 2,3-dihydrophenylindole may be removed by stirring with palladium in boiling xylene.[24]



Oxidation with permanganate readily opens the ring. Amorphous masses result unless the imino system is protected by benzoylation.[18] The product is benzoylanthranilic acid which by hydrolysis changes to anthranilic acid.

The dihydro-N-benzoyl derivative undergoes ring opening[25] also when chlorinated with phosphorus pentachloride at 150 to 160° and changes to the imide chloride. In the illustration below, the product of these steps, after hydrolysis, is benzoyl-*o*-(β-chloroporpyl)-anilide.

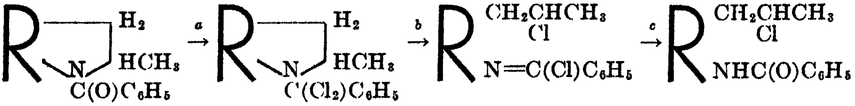
---

[22] v. Braun and Sobecki, *Ber.*, **44**, 2159 (1911).

[23] (*a*) v. Braun and Bayer, *ibid.*, **58**, 387 (1925); (*b*) Willstätter and Jacquet, *ibid.*, **51**, 767 (1918).

[24] Adkins and Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

[25] v. Braun and Steindorff, *Ber.*, **37**, 4581 (1904).



ᵃ PCl_5. ᵇ Heat (−HCl). ᶜ H_2O.

This method was mentioned in the case of pyrroles. It is a general reaction, the result of v. Braun's discovery[26] of a method for eliminating alkyl groups from a secondary amine. The amine is benzoylated or aroylated, and the amide thus formed is chlorinated with phosphorus pentachloride. The dichloride product will decompose in two steps, depending on the temperature.

$$C_6H_5C(Cl_2)NRR' \xrightarrow{110\text{—}130°} C_6H_5C(Cl){=}NR' + RCl$$

$$C_6H_5C(Cl){=}NR' \xrightarrow{160\text{—}170°} C_6H_5C{\equiv}N + R'Cl$$

If either R or R′ is aromatic, the first step only of pyrolysis results, and the chloramine product then undergoes partial hydrolysis to a substituted anilide or complete hydrolysis to a primary amine. The reaction is therefore a means for converting a secondary to a primary amine. The first application of this method for the opening of a cyclic amine was made to piperidine and to tetrahydroquinoline[27] and shortly thereafter to 2-methyldihydroindole.[25]

Indoles show the pine-splinter test of pyrroles. Ehrlich's test[28] for indole is the pink color formed with *p*-dimethylaminobenzaldehyde in the presence of 12 per cent hydrochloric or 85 per cent phosphoric acid. Since other compounds may interfere, the indole must be separated by steam distillation or by extraction with chloroform. Picrates and styphnates are useful for characterization, as is also the bisulfite compound.

Compounds.—*Indole* (m.p. 52°, b.p. 254 d.) is present in the coal-tar fraction that boils from 220 to 260°. Separation is effected by bisulfite, or by treatment with sodamide[29] at 150 to 160°, or with sodium hydroxide at 190 to 200°, after phenolic bases have previously been removed by aqueous sodium hydroxide. Any N-sodio derivative thus obtained can be treated with water, methyl iodide, benzoyl chloride, or with carbon dioxide at 190 to 200° to give indole, skatole, N-benzoylindole, or indolecarboxylic acid, respectively.

---

[26] v. Braun, *ibid.*, **37**, 2812 (1904).

[27] v. Braun, *ibid.*, **37**, 2915, 3210 (1904).

[28] Ehrlich, *Deut. med. Wochschr.* 1, (1901); Chernoff, *Ind. Eng. Chem., Anal. Ed.*, **12**, 273 (1940).

[29] Weissgerber, *Ber.*, **43**, 3520 (1910).

Indole is widely distributed. The presence of 1 to 2 per cent of indole in α-methylnaphthalene, another coal-tar product, is responsible for the red color that develops in the practical grade of that compound.[30] Perfumes, both natural and synthetic, contain small amounts as a valuable ingredient, although indole itself has a naphthylamine-like odor. Jasmine flowers, for example, contain 2½ per cent indole,[31] together with 3 per cent jasmone, 0.5 methyl anthranilate, 65 per cent benzyl acetate, 7.5 per cent linalyl acetate, 6.0 per cent benzyl alcohol, and 15.5 per cent linalool. The picrate is used to isolate indole from this mixture. Orange-blossom oil[32] contains approximately 0.1 per cent. Butter[33] made from decomposed cream shows a relatively high indole content. The compound is present in many bacterial processes, in the feces of dogs, and frequently in the feces of man.[34]

The formula of indole was originally deduced from its relationship to pyrrole and then was confirmed by preparation[35] from cinnamic acid, by the steps of nitration, reduction of the ortho product, and ring closure.

Other principal methods for its preparation are (*a*) by Fischer's synthesis from acetaldehyde; (*b*) by treatment of *o*-formotoluidide with potassium or potassium amide in liquid ammonia (about 50 per cent yield), with *t*-butoxide[36] in a metal bath at 360 to 380° (about 63 to 79 per cent yield), or by fusion of the sodium salt of phenylglycine-*o*-carboxylic acid[37] with two parts of alkali at 280 to 290°. This last method employs intermediates used in the synthesis of indigo.

Electrolytic[27] or catalytic reduction over nickel[38] converts indole to dihydroindole. Sulfur at 115 to 125° for 2 days gives β,β′-bisindolyl[39] (m.p. 286 to 287°). Methylmagnesium halide forms indolylmagnesium halide, and this product in turn reacts with chloroacetonitrile to give β-indolylacetonitrile.[40]

2-*Methylindole* (m.p. 59°, b.p. 119 to 126°/4 mm.) is prepared by methods analogous to those used for indole. For example, acetyl-*o*-toluidine gives an almost pure product in 80 to 83 per cent yield when heated with sodium amide[41] at 240 to 260° in an atmosphere of nitrogen.

---

[30] Kharasch, Kane, and Brown, *J. Am. Chem. Soc.*, **62**, 2242 (1940).

[31] Hesse, *Ber.*, **32**, 2611 (1899); **33**, 1585 (1900).

[32] Hess and Zeitschel, *J. prakt. Chem.* [2], **66**, 481 (1902).

[33] Clarke, *et. al.*, *J. Assoc. Official Agr. Chem.*, **20**, 481 (1937).

[34] Herter, *J. Biol. Chem.*, **4**, 101 (1908).

[35] Baeyer and Emmerling, *Ber.*, **3**, 514 (1870).

[36] Tyson, *J. Am. Chem. Soc.*, **63**, 2024 (1941); *Org. Syntheses*, **23**, 42 (1943).

[37] D.R.P. 85071.

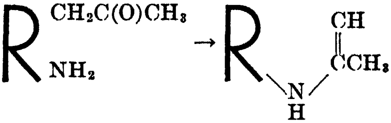
[38] Carrasco and Padoa, *Gazz. chim. ital.*, **36**, II, 512 (1906).

[39] Oddo and Raffa, *Gazz. chim. ital.*, **69**, 562 (1939).

[40] Majima and Hoshino, *Ber.*, **58**, 2042 (1925).

[41] Allen and Van Allan, *Org. Syntheses*, **22**, 94 (1942).

Sodium ethoxide gives a yield of 60 per cent. Nitration of α-phenylacetone, reduction of the *o*-nitro product, and removal of water also give the 2-methyl homologue.[14b]



3-*Methylindole* (m.p. 95°, b.p. 266°/255 mm.), commonly called "skatole" from τὸ σκατὸς, meaning "feces," is the odoriferous constituent[42] of human feces. Among a variety of methods, it is probably best prepared (74 per cent yield) from the phenylhydrazone of propionaldehyde.[3,43] It can be obtained also from indolylmagnesium iodide and methyl iodide.[44]

The quantity of skatole[34] present in human feces varies with the age and healthiness of intestinal digestion. That from healthy children under ten seldom has any. From older individuals, there is usually not more than 0.0005 per cent sometimes increasing to 0.008 and 0.01 per cent. Skatole has been found also in *Celtis reticulosa*, a large tropical tree growing in Java, known locally by the Java equivalent of filth wood. The content is possibly less than 0.1 per cent. The fact that it is present only in old wood of the trunk, or in wounded branches, suggests that it is the product of some microorganism.[45] Civet,[46] a secretion from the African civet cat, used as a base in perfumes, contains about 0.1 per cent of skatole.

Skatole is distinguished chemically from indole by the absence of an active methylene group in the pseudoindole form. Hence skatole gives no red color with sodium nitrite nor the blue-green color characteristic of the reaction of indole with sodium naphthoquinonesulfonate.[47]

4-*Methylindole*[48] is found, together with the 2- and 7-isomers, in coal tar. 5-*Methylindole* (m.p. 58.5°) is derived by pyrolysis of 5-methylindole-2-carboxylic acid,[49] itself secured by a Fischer indole synthesis from *p*-tolylhydrazine and pyruvic acid. 7-*Methylindole* (m.p. 85°)[50] is derived by similar steps from *o*-tolylhydrazine. The N-methyl isomer is formed from indolylsodium and methyl iodide.

---

[42] Brieger, *Ber.*, **10**, 1028 (1877); *J. prakt. Chem.* [2], **17**, 124 (1878).

[43] Arbusow and Tichwinsky, *Ber.*, **43**, 2302 (1910).

[44] Oddo, *Gazz. chim. ital.*, **41**, I, 221 (1911).

[45] Herter, *J. Biol. Chem.*, **5**, 489 (1909).

[46] Walbaum, *Ber.*, **33**, 1903 (1900).

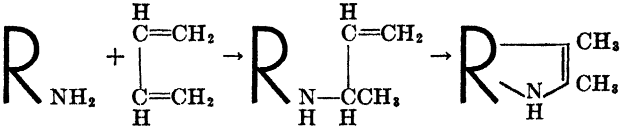
[47] Herter and Foster, *J. Biol. Chem.*, **1**, 257 (1906); **2**, 267 (1906).

[48] Kruber, *Ber.*, **59**, 2752 (1926); **62**, 2877 (1929).

[49] Robson, *J. Biol. Chem.*, **62**, 495 (1924).

[50] Boyd and Robson, *Biochem. J.*, **29**, 555 (1935).

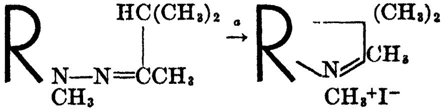
2,3-*Dimethylindole* (m.p. 105 to 106°) is made[51] from the phenylhydrazone of methylethyl ketone and zinc chloride at 180°. Quantities of less than 1 per cent are formed[52] when aniline, aniline hydrochloride (but not the hydrobromide), and butadiene are condensed together. The action appears to be a 1,2-addition of the amine to butadiene followed by a ring closure.



p-Toluidine, in a similar way, yields 2 per cent of 2,3,5-trimethylindole. The normal reaction with the diene is, of course, 1,4-addition, to give either a secondary amine, $C_6H_5NH(C_4H_6)H$, or a primary amine, $H_2NC_6H_4(C_4H_6)H$. 2,3-Dimethylindole does not respond to the pine-splinter test but does yield a yellow nitroso derivative (m.p. 63°) and shows a positive Liebermann reaction.

2-*Phenylindole* (m.p. 188 to 189° corr.) is best obtained[53] in about 80 per cent yield from acetophenonephenylhydrazone and anhydrous zinc chloride at 170°. It is formed also when benzoyl-*o*-toluidine is heated with sodium pentoxide, $NaOC_5H_{11}$.

Pseudoindoles, sometimes called "indolenines," are prepared by alkylation of appropriate indoles or by synthesis of the heterocyclic ring. For example, the methiodide of 2,3,3-trimethylindole[54] forms by complete alkylation of methyl-, N-methyl-, or 2,3-dimethyl-indole with methyl iodide in hot methanol. It can be prepared also from unsymmetrical phenylmethyl hydrazine and methyl isopropyl ketone by means of Fischer's synthesis.



[a] HI in methanol.

The methiodide, when warmed, loses methyl iodide and gives 1,2,3-trimethylindole; when treated with alkali, it loses hydriodic acid and gives a base that oxidizes easily in air to a rose-red color and has the methylene group[55] as represented below. Alkaline permanganate converts this last compound to 1,3,3-trimethylindolinone-2, a reaction that shows the position of the double bond. Hydriodic acid converts the 2-methylene compound to the original salt.

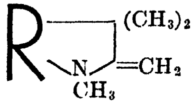
---

[51] Fischer, *Ann.*, **236**, 116 (1886).

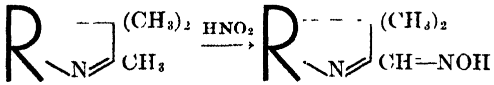
[52] Hickenbottom, *J. Chem. Soc.*, 1981 (1934).

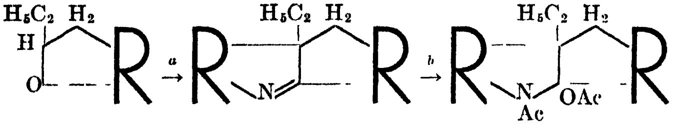
[53] Shriner, Ashley, and Welch, *Org. Syntheses*, **22**, 98 (1942).

[54] Fischer and Steche, *Ann.*, **242**, 348 (1887); Ciamician and Plancher, *Ber.*, **29**, 2475 (1896); Brunner, *ibid.*, **31**, 612, 1943 (1898); Plancher and Carrasco, *Atti accad. Lincei* [5], **14**, II, 31 (1905).



The C=N group in pseudoindole behaves as does an aldehyde group, and so activates the adjoining methyl group that an oxime is formed from the reaction with potassium nitrite, as illustrated in the case of 2,3,3-trimethyl-ψ-indole below. The C=N group also adds[56] amines, ammonia, or acetic anhydride as aldehydes generally do. For example, the ethyl-*o*-benzylenindolenine compound, which is made from ethylhydrindone as shown below, will add acetic anhydride in the presence of sodium acetate.





[a] Formation of the hydrazone by condensation with phenylhydrazine at 100° in the presence of sodium acetate followed by a Fisher indole synthesis with $ZnCl_2$. [b] Acetic anhydride and sodium acetate at 100°.

When the diacetyl derivative is warmed to 60° for 10 min. with 12 *N* hydrochloric–acetic acid, the ester is hydrolyzed to the hydroxy-N-acetyl derivative; if heated with methanol, the acetoxy is replaced by a methoxy group; if treated with benzoic anhydride and sodium benzoate at 100°, both acetyl groups are replaced by benzoyl radicals.[57]

The bisulfite addition compound,[29,31] which forms when indole is shaken with 40 per cent bisulfite solution, may be due to this ψ indole form, if the analogy with aldehydes is valid. (For a discussion of ammono aldehyde systems in other rings, see page 194.) The indole is recovered by warming with aqueous sodium carbonate.

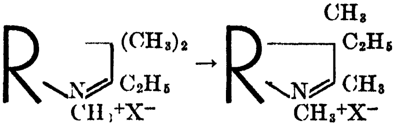
---

[55] Hantzsch and Horn, *Ber.*, **35**, 883 (1902); Decker and Klauser, *ibid.*, **37**, 524 (1904).

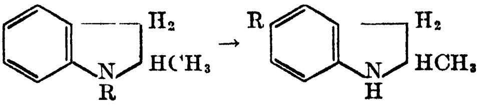
[56] Plancher, *ibid.*, **31**, 1488 (1898); Plancher and Bettinelli, *Gazz. chim. ital.*, **29**, I, 106 (1899).

[57] Leuchs and Winzer, *Ber.*, **58**, 1520 (1925); Leuchs and Kowalski, *ibid.*, **58**, 2822 (1925); Leuchs, Philpott, Sander, Heller, and Köhler, *Ann.*, **461**, 27 (1928).

1,3,3-*Trimethyl-2-ethylindolenine iodide*, prepared either from methyl iodide and 3,3-dimethyl-2-ethylindolenine or from phenylmethylhydrazine and ethylisopropyl ketone, undergoes a novel rearrangement[58] to 1,2,3-trimethyl-3-ethylindolenine iodide when heated. A transitory separation of an alkyl iodide may be a factor in this change.



2,3-*Dihydroindoles*, often called "indolines," are obtained by reduction of indoles. They are comparatively strong bases because they are secondary amines and undergo the typical reactions[59] of such compounds. For example, nitrous acid converts them to N-nitroso derivatives, and these in turn undergo rearrangement in acid to *p*-nitroso products as illustrated below. Similarly, diazoamino compounds can be formed which rearrange[60] to azo products in the presence of acid. The N-nitroso compound[24] can be reduced also to a hydrazine by zinc dust and acetic acid. Reduced indoles also undergo ring cleavage when subjected to exhaustive methylation (see page 307).



R = NO or $N{=}NC_6H_5$.

Indoline (b.p. 230°; benzenesulfonyl derivative, m.p. 133°) can be synthesized from a *β*-(*o*-aminophenyl)ethyl alcohol and hydrochloric acid, maintained for 5 hr. at 130 to 140°, followed by treatment of the hydrochloride with sodium hydroxide. The necessary *o*-aminophenylethyl alcohol is obtained by nitration of *β*-phenylethyl alcohol and reduction of the nitrated product with zinc and aqueous calcium chloride solution.[61] This intermediate, incidentally, is suitable for the preparation of other related five-membered ring systems, *viz.*, dihydrobenzofuran and dihydrothionaphthene, by replacement of the amino with a hydroxyl or thio group, by means of the diazo reaction.

α-Aminoindole is obtained from *o*-aminobenzylcyanide and sodium ethoxide in boiling alcohol. The sequence[62] of necessary steps from *o*-nitrophenylacetic acid is shown below.

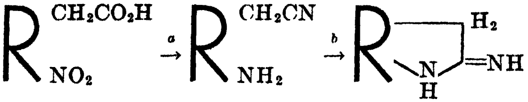
---

[58] PLANCHER and BONAVIA, *Gazz. chim. ital.* [11], **32**, 414 (1902).

[59] BAMBERGER and STERNITZKI, *Ber.*, **26**, 1291 (1893).

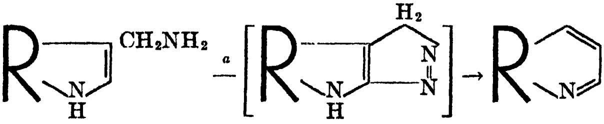
[60] BAMBERGER and ZUMBRO, *ibid.*, **26**, 1285 (1893).

[61] SABELAY, BLÉGER, and DE LESTRANGE, *Bull. soc. chim.* [4], **49**, 3 (1931).



[a] Sequence of $SOCl_2$, NH_3, P_2O_5 or $SOCl_2$, Sn + HCl. [b] NaOEt. The product undergoes tautomerism to the α-amino indole.

3-*Indolemethylamine* is prepared by reduction of β-cyanoindole. The compound undergoes an interesting ring enlargement to quinoline when treated with nitrous acid. The change may occur through an intermediate pyrazole compound as shown below by partial formulas. The fact[63] that 2-methyl-3-indolemethylamine yields the same quinoline

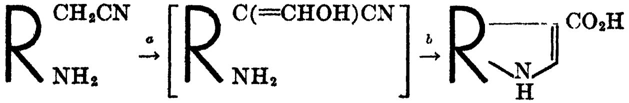


[a] HNO_2.

compound (*i.e.*, the α-methyl group is lost) conforms with such an explanation.

3-*Aldehydoindole* is made by a conventional chloroform and alkali treatment applied to indole.[50] The yield is 31 per cent. By a similar process, 2-methyl and 5-methylindoles give 51 and 27 per cent of the corresponding aldehydes.

Indole-β-carboxylic acid (m.p. 218°) is obtained[64] when a mixture of indole and sodium is heated in a stream of carbon dioxide at 230° up to 300°, after the manner of a Kolbe synthesis. It may also be obtained[62] from the *o*-aminophenylacetonitrile, mentioned in a preceding paragraph, by condensation of the nitrile with sodium and amyl formate, ring closure, and hydrolysis of the resulting β-cyanoindole.



[a] Na + $C_5H_{11}O_2CH$. [b] Hydrolysis of the nitrile.

Indole-3-acetic acid (m.p. 164 to 165°), known also as "heteroauxin," is prepared conveniently by a Japp-Klingemann synthesis[65] from benzene-diazonium chloride and ethyl α-acetylglutarate, followed by hydrolysis and controlled decarboxylation of the diacid product. Skatole is produced if decarboxylation is prolonged beyond the time when one mole equivalent of carbon dioxide has been evolved.

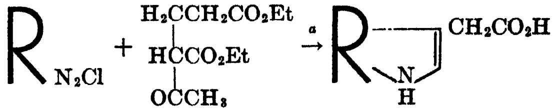
---

[62] Pschorr and Hoppe, *Ber.*, **43**, 2543 (1910).

[63] Putokhin and Davuidova, *J. Gen. Chem.* (*U.S.S.R.*) **2**, 290 (1932); *C.A.*, **27**, 722 (1933).

[64] Zatti and Ferratini, *Ber.*, **23**, 2296 (1890).

[65] King and L'Ecuyer, *J. Chem. Soc.*, 1901 (1934).



[a] The acetylglutarate (from β-iodopropionic ester and ethyl sodioacetoacetate) is converted to the hydrazone, which is then converted to the indole with HCl in abs. alc. The diester is then hydrolysed and the diacid decarboxylated over quinoline and copper to give the monoacid product.

Heteroauxin causes elongation of plant cells; its unequal distribution in a plant causes phototropism and geotropism. It was the first of such agents, of known structure, to be discovered.

The discovery of heteroauxin is one of the interesting adventures in chemistry. By a long series of operations that involved extraction, precipitation with lead acetate and calcium acetate, and high-vacuum distillation, Kögl[66] and coworkers were able to separate from urine a crystalline material that stimulated cell elongation. This material was called "auxin." Subsequently[67] the same material, in much less quantity, was found in corn oil, together with another one, which was designated auxin *b*. In order to secure a large quantity of auxin *a*, urine was collected from hospitals. Although this material showed a high auxin activity, the usual method of separation failed to produce the expected quantity of crystalline material. The active substance, when eventually separated,[68] proved to be β-indolylacetic acid. Because it was different from auxin *a* and *b*, it was called "heteroauxin." Normal individuals excrete auxin and heteroauxin in the proportions of about 4 to 1. In hospital urine, the proportions may be reversed because of greater intestinal putrefaction caused by a diminished food intake and by less auxin in the diet.

Indole-3-acetic acid is now merely one among a large number of compounds known as plant hormones. The class includes other closely related heterocyclic compounds such as the 1-, 2-, or 5-methylindoleacetic acids, indole-3-α-propionic, and indole-3-pyruvic acid. Many nonheterocyclic compounds are now known to have a similar effect. Among these are phenylacrylic acid, phenylpropionic acid, and naphthaleneacetic acid. Inactive indole acids[69] are dihydroindole-3-acetic, 2-ethylindole-3-acetic, 2,5-dimethylindole-3-acetic, indole-2(or 3-)-carboxylic, and indole-3-β-propionic.

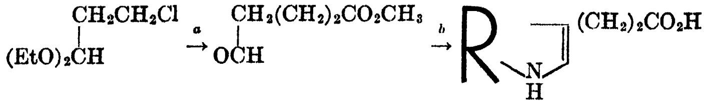
[66] Kögl, Haagen-Smit, and Erxleben, *Z. physiol. Chem.*, **214**, 241 (1933); **216**, 31 (1933).

[67] Kögl, Erxleben, and Haagen-Smit, *ibid.*, **225**, 215 (1934).

[68] Kögl, Haagen-Smit, and Erxleben, *ibid.*, **228**, 90 (1934).

[69] Pollard, *Ann. Repts.*, **32**, 425 (1936); Hitchkock and Zimmermann, *Contrib. Boyce Thompson Inst.*, **7**, 439, 447 (1935).

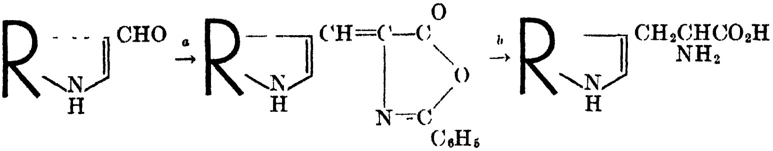
β-(Indolyl-3)propionic acid, $C_8H_6N{\cdot}CH_2CH_2COOH$, is one of the products present in the putrefaction of proteins. It is prepared[70] by a Fischer indole synthesis from an aldehydobutyric acid, itself made from β-chloropropionacetal and ethyl sodiomalonate.



[a] $NaCH(CO_2Et)_2$ followed by NaOH, HX, heat, and CH_3OH + HX. [b] $C_6H_5NHNH_2$, HX.

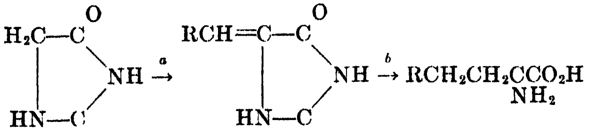
Tryptophan is α-amino-β-(indolyl-3-)propionic acid. It is a product of the putrefaction of proteins[71] and disappears in the later stages in which indolylpropionic acid, indoleacetic acid, indole, and skatole appear. By careful adjustment of conditions, this amino acid intermediate product can be derived from casein.[72]

Tryptophan can be synthesized[73] by a sequence of steps that starts with β-indolylaldehyde and hippuric acid and progresses to the final stage by hydrolysis and reduction of the azlactone product. The reaction is common for the preparation of α-amino acids.



[a] Hippuric acid + Ac_2O + NaOAc. [b] Hydrolysis with alkali to give indolyl-α-benzoylaminoacrylic acid followed by reduction with Na + EtOH.

A preparation from hydantoin is somewhat similar.[74]



R = indolyl radical.
[a] 3-Aldehydoindole with piperidine. [b] NH_4SH, + NH_4OH at 100 to 103°.

Tryptophan[73] is readily oxidized by a 10 per cent solution of ferric chloride to β-indolaldehyde. Oxidation by permanganate leads to β-indolecarboxylic acid. These reactions were used originally to determine the structure of this compound. Tryptophan is detected by the

---

[70] Ellinger, *Ber.*, **38**, 2884 (1905).

[71] Hopkins and Cole, *J. Physiol.*, **27**, 420 (1901); **29**, 438, 451 (1903); Mitchell and Hamilton, "Biochemistry of Amino Acids," Reinhold Publishing Corporation, New York, 1929.

[72] Cox and King, *Org. Syntheses, Coll. Vol.* II, 613 (1943).

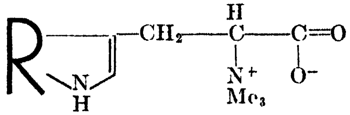
[73] Ellinger, *Ber.*, **39**, 2515 (1906); Ellinger and Flamand, *ibid.*, **40**, 3029 (1907).

[74] Boyd and Robson, *Biochem. J.*, **29**, 2256 (1935).

Hopkins-Cole test, which is the occurrence of a violet color when treated with a sulfuric–glacial acetic acid solution of glyoxylic acid. The same acid, but with sulfuric acid and copper sulfate, can be used for a quantitative estimation[75] provided the color is compared in a colorimeter with that of a solution of known tryptophan content and the test is made by a definite procedure. The dl form melts at 283 to 285°.

The amount of tryptophan[76] in fresh casein is 1.33 to 1.25 per cent and 1.09 and 0.92 in older samples. It is widely distributed in nature. Its varying quantity in different materials, such as the tobacco and cucumber virus, is sometimes a means to distinguish between different varieties.

Hypaphorine is the betaine[77] of tryptophan. It occurs in the seeds of *Erythrina hypaphorous*.

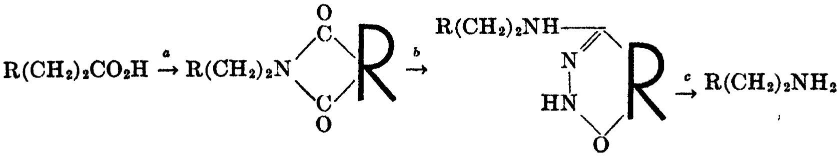


Tryptamine, or 3-indolylethylamine, $C_8H_6N{\cdot}CH_2CH_2NH_2$, is the product of decarboxylation of tryptophan. It is prepared[78] by cautious heating of a mixture of phenylhydrazine and the acetal of γ-aminobutyraldehyde until a vigorous exothermic reaction ensues.

$$C_6H_5NHNH_2 + (EtO)_2CH—(CH_2)_3NH_2{}^{a} \xrightarrow{ZnCl_2} C_8H_6NHCH_2CH_2NH_2$$

[a] Prepared from acrolein and hydrogen bromide in absolute alcohol, followed by reaction with sodium cyanide and then reduction of the nitrile.

It may also be obtained by a series of steps from β-(indolyl-3)-propionic acid, which consists of a Curtius degradation of the azide, formation of the urea derivative from the cyanate, conversion to the phthalimide, and hydrolysis via the hydrazine process.[79a] This last step is an improvement over the conventional hydrochloric acid–sealed tube hydrolysis of the imide, which causes complete resinification of this compound.



Small R = indolyl radical; large R = benz system.

[a] Conversion of the acid to an amine by successive use of $SOCl_2$, NaN_3, HX, H_2O followed by reaction with phthalic anhydride. [b] H_2NNH_2. [c] HX + H_2O.

---

[75] Shaw and McFarlane, *Can. J. Research, Sec. B.*, **16**, 361 (1938).

[76] Knight and Stanley, *J. Biol. Chem.*, **141**, 39 (1941).

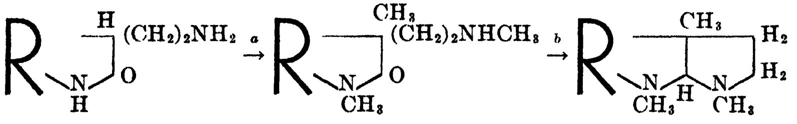
[77] Van Romburgh and Barger, *J. Chem. Soc.*, **99**, 2068 (1911); Harrington, *ibid.*, 715 (1939).

[78] Ewins, *ibid.*, **99**, 270 (1911).

[79] (*a*) Manske, *J. Am. Chem. Soc.*, **51**, 1202 (1929); (*b*) Manske, *Can. J. Research*, **5**, 592 (1931).

N-Methyltryptamine is an integral part of the alkaloid *calycanthine* from which it is obtained as the benzoyl derivative by degradation. It can be prepared[79b] by methylation of tryptamine with methyl iodide or by pyrolysis of the quaternary metho chloride in vacuum.

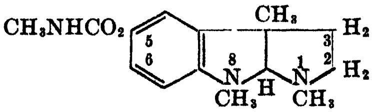
Oxytryptophan, $C_6H_4\left\{\begin{array}{c}\text{—CH}\\ \text{NH}\dot{\text{C}}\text{O}\end{array}\right\}\begin{array}{c}CH_2CHNH_2\\ CO_2H\end{array}$ may be a transformation product in the intermediary metabolism of tryptophan in animals.[80] Decarboxylation gives oxytryptamine. Methylation of oxytryptamine with methyl iodide and alkoxide gives the trimethyl derivative. Reduction of this trimethyl derivative with sodium and alcohol gives simultaneous ring closure and formation of a tricyclic compound related to physostigmine. These steps are shown below.



a CH_3I + NaOEt. b Na + EtOH. Large R = C_6H_4.

Physostigmine, sometimes better known as "eserine," is a resinous and poisonous alkaloid in the Calabar bean. This bean is known also as the "ordeal" or "test bean"[81] because the natives of West Africa used it in their trials of crime and witchcraft. An innocent person, unafraid of the test, might happen to swallow the poison rapidly and suffer gastric irritation and vomiting that automatically spared him; a guilty defendant, afraid of the test, might happen to eat slowly, retain the poison and die. Any deviation from this principle would lead to a miscarriage of justice. It has been used some in medicine to cause bowel evacuation and to treat tetanus and epilepsy and is valuable in ophthalmic surgery because it causes the pupils to contract.

The formula, shown below, can be regarded as a three-ring addition product of a substituted methylaniline, methyl amine, and isoprene. This structure was first proposed by Stedman and Barger[82] after consideration of the degradation products. Pyrolysis, for example, at 200° in an atmosphere of carbon dioxide yielded physostigmol, later shown to



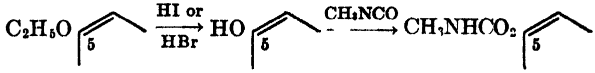
---

[80] Julian and Pikl, *J. Am. Chem. Soc.*, **57**, 755 (1935).

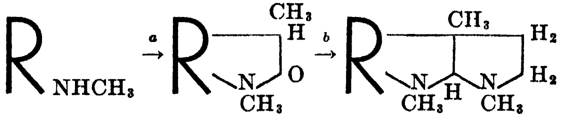
[81] Goodman and Gilman, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

[82] Stedman and Barger, *J. Chem. Soc.*, **127**, 247 (1925).

be 5-hydroxy-1,3-dimethylindole-3-acetic acid. Preparation of the ethyl[83] and methyl[84] ether of physostigmol established the presence of the indole nucleus and the orientation of certain substituents.[85] The ethyl ether, called "eserethole," is readily[85] converted to eserine by the following steps, shown by partial formulas.



The synthesis of eserethole from N-methyl-p-phenetidine[80] and α-bromopropionyl bromide as starting reagents is shown below.

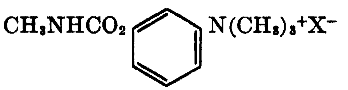


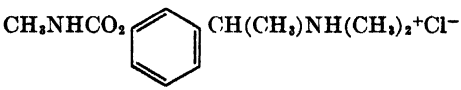
Large R = $C_2H_5OC_6H_{3 \text{ or } 4}$ < with ethoxy group para to nitrogen.

[a] $BrC(O)CH(Br)CH_3$, heat, $AlCl_3$. [b] Et_2SO_4 (to restore ethoxy group which was cleaved to hydroxy by $AlCl_3$), $ClCH_2CN$ + NaOEt, Pd + H_2 (to prepare amine), C_6H_5CHO (to obtain anil), CH_3I in sealed tube (Dakin's method for monomethylation of an amine), α-camphorsulfonic acid and α-tartaric acid (to separate optical isomers), Na + EtOH to reduce the carbonyl group and close ring.

Deoxyeseroline is the oxygen-free eserine. It is prepared[86] from dimethyloxindole, which is the same as the second compound in the above sequence of formulas except for the absence of an ethoxy group. The formation of a third ring occurs more readily than before and requires only the use of chloroacetonitrile and sodium ethoxide, hydrogen for reduction, ring closure, and methyl iodide.

Efforts to find substitutes for physostigmine have had much success. Urethanes,[87] of the types shown below, have marked activity whereas the o- and p-isomers do not.





These compounds are structurally unlike physostigmine, which has an amino group in the position para to the oxygen atom. If, however, an alkyl group is introduced in the benzene ring—and physostigmine can be regarded as an alkyl substituted p-aminophenol derivative—both the o- and p-products become active.[88]

---

[83] STEDMAN, *ibid.*, **125**, 1373 (1924).

[84] SPÄTH and BRUNNER, *Ber.*, **58**, 518 (1925).

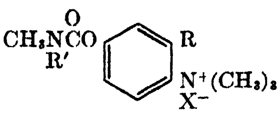
[85] KING and ROBINSON, *J. Chem. Soc.*, **755**, (1935).

[86] JULIAN, PIKL, and BOGGESS, *J. Am. Chem. Soc.*, **56**, 1797 (1934).

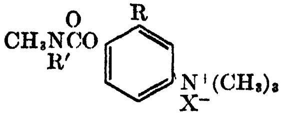
[87] STEDMAN, *Biochem, J.*, **20**, 719 (1926); **23**, 17 (1929); STEDMAN and STEDMAN, *J. Chem. Soc.*, 609 (1929).

[88] STEVENS and BENTEL, *J. Am. Chem. Soc.*, **63**, 308 (1941).

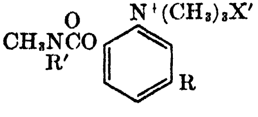
A



B



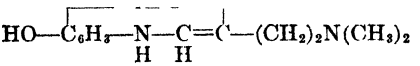
C



R′ = H or CH_3.

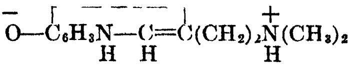
Judged by the amount necessary for a lethal dose in mice, dimethylurethanes (R′ = CH_3) of these types are less active than monomethyl compounds. An isopropyl group (R in type A) increases the activity 1,600 fold over the parent compound (R = H). When R = CH_3, the type C formula is most active; when R = isopropyl, the type A formula is best.

Bufotenine, β-(5-hydroxyindolyl)ethyldimethylamine, is one among a considerable number of toad poisons, many of which are sterols.[89] The compound was isolated by Wieland[90] and coworkers who subjected the extracts from toad skins to chromatographic adsorption. Bufotenine is found with the isomeric bufotenidine, a betaine.



$HO-C_6H_3-\underset{H}{N}-\underset{H}{C}=C-(CH_2)_2N(CH_3)_2$

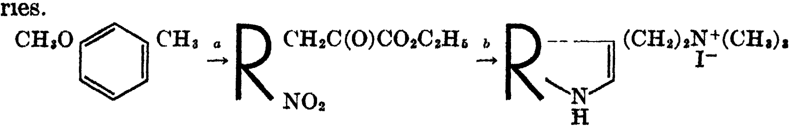
Bufotenine



$\overset{-}{O}-C_6H_3\underset{H}{N}-\underset{H}{C}=C(CH_2)_2\underset{H}{\overset{+}{N}}(CH_3)_2$

Bufotenidine

The structure was suggested by (*a*) the presence of an indole nucleus, shown by characteristic test; (*b*) the presence of a phenolic hydroxyl group that was judged to be in the 5-position, a favored one in most naturally occurring products; (*c*) the presence of a dimethylamino group attached to one of the two carbon atoms outside the indole nucleus, shown by elimination of nitrogen in one step of exhaustive methylation; (*d*) the absence of a substituent in the 2-position as judged by the positive Hopkins-Cole glyoxylic acid test; and (*e*) the possible similarity to the naturally occurring tryptophan. This opinion was confirmed by synthesis of the O-methyl ether of bufotenien methiodide. The synthesis shown below follows the general pattern of many condensations in this series.



Large R = $CH_3OC_6H_3$. The methoxy group is para to the nitrogen atom.

[a] HNO_3, $(CO_2Et)_2$ + NaOR. The nitro group activates the CH_3 so that condensation occurs readily. [b] $FeSO_4$ + NH_3, ring closure, decarboxylation of the carboxylic acid, CH_3MgI, $ClCH_2CN$, Na + alcohol, CH_3I + thallium ethoxide.

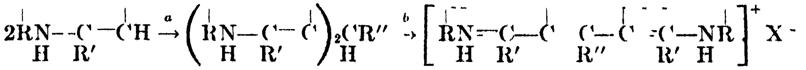
Rosindoles.—Aldehydes and α-substituted indoles[91] form condensation products analogous to the triphenylmethanes. Oxidation converts the methanes to dyes that are analogous to fuchsin and are known as "rosindoles."

---

[89] Friedmann, "Sterols and Related Compounds," Reinhold Publishing Corporation, New York, 1937.

[90] Wieland, Konz, and Mittasch, *Ann.*, **513**, 1 (1934).

[91] Fischer, *Ber.*, **19**, 2988 (1866); *Ann.*, **242**, 372 (1887); Walthor and Clemen, *J. prakt. Chem.* [2], **61**, 249 (1900).



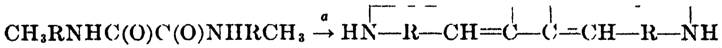
$$2\underset{H}{RN}-\underset{R'}{C}-CH \xrightarrow{a} \left(\underset{H}{RN}-\underset{R'}{C}-C\right)_2\underset{H}{C}R'' \xrightarrow{b} \left[\underset{H}{RN}=\underset{R'}{C}-C \quad \underset{R''}{C}-C=\underset{R'}{C}-\underset{H}{NR}\right]^+ X^-$$

R = C_6H_4. R′ = alkyl or other common substituent in the alpha position. R″ = alkyl or aryl.
[a] R″CHO. [b] Oxidation followed by treatment with HX.

Similar compounds can be prepared[92] in very good yields by the action of indolylmagnesium derivatives on aldehydes.

Formation of rosindoles may be related to fixation of perfumes[93] by musk, ambergris, benzyl salicylate, indole, skatole, etc. When mixtures of indoles (0.1 g.) and various aldehydes (2 g.) in ethyl alcohol are allowed to stand in closed bottles in diffused light for one year and then in sunlight for another year, progressive chromatic changes occur that are greatest with α-methylindole, less with indole, and least with skatole. This order parallels the case of formation of rosindoles from these three compounds.

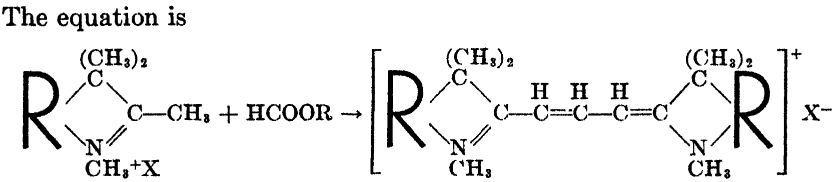
Diindolyl(2,2′) or α,α′-diindyl[94] is obtained from the di-*o*-toluidide of oxalic acid with sodium pentoxide in amyl alcohol in an inert atmosphere at 360° (see pages 103, 109). The compound melts at 302 to 303° and forms a 3,3′-diisonitroso derivative, which by reduction with sodium hydrosulfite gives a diamino compound which in turn changes readily to indigo by oxidative hydrolysis.



$$CH_3RNHC(O)C(O)NHRCH_3 \xrightarrow{a} HN-R-CH=C-C=CH-R-NH$$

R = C_6H_4.
[a] $NaOC_5H_{11}$.

Indolenine red is obtained by condensation of a methylene base, of the type already discussed under indolenines, with esters of formic acid. The equation is



The CN function in the ring, like a nitro group, makes the CH_3 react readily.

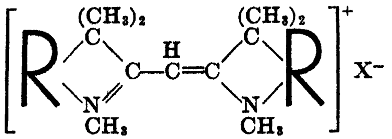
The constitution is analogous to that of the cyanine dyes; and the reaction is typical of cyanine dye formation. The same reaction with nitrous acid instead of the formate gives indolenine yellow[94] with loss of hydrogen cyanide during condensation.

---

[92] MINGOIA, *Gazz. chim. ital.*, **56**, 772 (1926); *C.A.*, **21**, 1117 (1927).

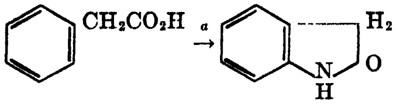
[93] MADELUNG, *Ann.*, **405**, 58 (1914).

[94] KUHN, WINTERSTEIN, and BALSER, *Ber.*, **63**, 3176 (1931).



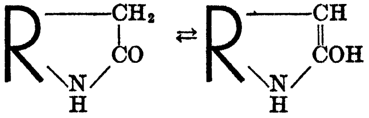
OXYGENATED INDOLE COMPOUNDS

Oxindole (m.p. 126°) was mentioned at the beginning of this chapter as a reduction product of isatin. The original synthesis of Baeyer[95] from phenylacetic acid consists of a sequence of nitration, reduction, and dehydration.[96] This interesting compound may also be prepared by condensation of *o*-nitrotoluene[97] with ethyl oxalate under the influence of sodium ethoxide and oxidation (H_2O_2) of the phenylpyruvic acid product. The preparation from chloroacetanilide[98] and aluminum chloride at 225° can be used for the homologues of oxindole, but not for benz-substituted compounds such as would be derived from naphthylamine.



[a] HNO_3, Sn + HCl or $FeSO_4$ + NH_3, Heat.

Oxindole contains two active hydrogen atoms according to the Zerewittenov test. The formula may, therefore, be represented as a tautomeric system.



The reactions are, however, largely those of the form on the left. Ethyl iodide[99] and alcoholic sodium ethoxide, for example, give N-ethyloxindole. Oxindole is also a cyclic amide. Hot (150°) aqueous barium hydroxide opens the ring to give the barium salt of *o*-aminophenylacetic acid; acid re-forms the oxindole.[100]

By far the largest number of reactions involve the methylene group[98,99] which is active because it is flanked by a phenyl and carbonyl group. Nitrous acid gives the oxime, $\overline{C_6H_4NHC(O)C}{=}NOH$, which is reductible to the amine; *p*-nitrosodimethylaniline gives the corresponding anil; and benzaldehyde forms the benzylidene oxindole, $\overline{C_6H_4NHC(O)C}{=}CHC_6H_5$, when allowed to react with a hot alcoholic solution in the presence of piperidine. Similarly, *m*-nitrobenzaldehyde, anisaldehyde, piperonal, and other compounds with an active carbonyl group condense readily. The products are known by the class name of "isoindogenides"[101] (page 125).

---

[95] Baeyer, *ibid.*, **11**, 582 (1878).

[96] Heller, *ibid.*, **49**, 2777 (1916).

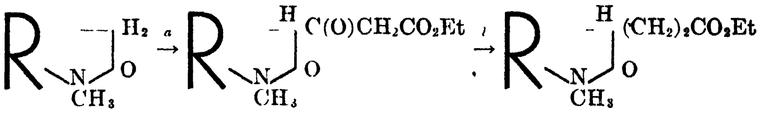
[97] Heissert, *ibid.*, **30**, 1030 (1897); **41**, 3925 (1908).

[98] Stollé, Bergdoll, Luther, Auerhahn, and Wachu, *J. prakt. Chem.* [2], **128**, 1 (1930).

[99] Baeyer and Comstock, *Ber.*, **16**, 1704 (1883).

[100] Marschalk, *ibid.*, **45**, 585 (1912); *J. prakt. Chem.* [2], **88**, 227 (1913).

Reactivity of the β-hydrogen atom is shown also by N-methyloxindole. For example, sodium ethoxide[102] causes the oxindole to condense with ethyl malonate to give a keto ester, which can be reduced catalytically to ethyl β-(1-methyloxindolyl-3)-propionate. Similarly, ethyl formate



^{a} NaOEt + H_2CCO_2Et. ^{b} Pd + H_2.

yields the 3-aldehydo derivative.[86] Attempts to replace the second hydrogen atom by a methyl group from methyl iodide and sodium methoxide cause, however, the replacement of the aldehydo group and formation of 1,3,3-trimethyloxindole.

Halogenation of oxindoles can be made to occur in either the homo- or hetero-cyclic ring, depending on the substituents and conditions. Bromine and potassium bromide give the 5-monobromo and, in hot water, the 5,7-dibromooxindole.[98] Phosphorus penta- and oxy-chloride mixture[103] forms 2,3-dichloroindole. When the imino hydrogen is replaced by an alkyl group, as in 1-ethyloxindole, bromination (*a*) in carbon tetrachloride at 0° gives an addition product that changes to the 3,3-dibromo compound[98] when warmed, and (*b*) in aqueous solution gives the 5-bromo compound. Calcium hypochlorite with N-methyloxindole gives the 3,3-dichloro-product which is readily hydrolyzed by aqueous-alcoholic sodium hydroxide to isatin. The position of these two halogen atoms can be shown also by synthesis of the 3,3-dichloro compound from trichloroacetmethylanilide, itself obtained from trichloroacetyl chloride and methyl aniline.

Indoxyl is an intermediate in the synthesis of indigo. The methods for preparation of that dye are invariably directed toward indoxyl. Some of the syntheses are listed in Fig. 3. The first of these, *viz.*, that from ethyl-*o*-nitrophenylpropiolate, via the intermediate indoxylic acid, is the one discovered by Baeyer. Baeyer did not isolate[104] a pure indoxyl. He merely decarboxylated indoxylic acid and observed that a product was obtained which rapidly changed to indigo. It remained for Vorländer and Drescher,[105] 20 years later, to carry out this decarboxylation in 20 parts of water at 70 to 80° and to allow the bright yellow prismatic crystals to separate when the solution was cooled in ice.

---

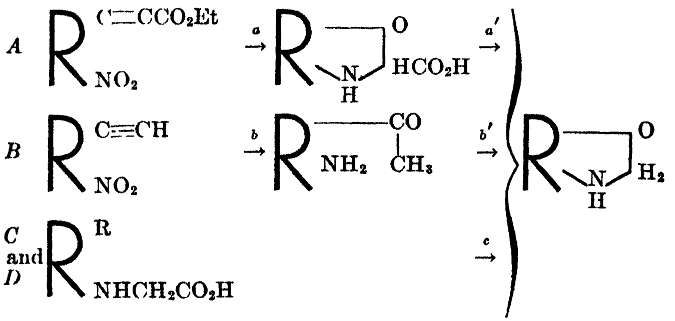
[101] Wahl and Bagard, *Bull. soc. chim.* [4], **5**, 1033 (1909).

[102] Julian, Pikl, and Wantz, *J. Am. Chem. Soc.*, **57**, 2026 (1935).

[103] Baeyer, *Ber.*, **12**, 456 (1879).

[104] Baeyer, *ibid.*, **14**, 1741 (1881).

The second method (Fig. 3) was likewise discovered by Baeyer.[106] *o*-Nitrophenylacetylene, prepared by decarboxylation of *o*-nitrophenylpropiolic acid, is reduced by zinc dust and ammonia to the *o*-amino compound. Water is added by means of dilute sulfuric acid. Dry bromine introduces a halogen in the ω-position (bromine in water or acetic acid introduces it in the nucleus), while the amino group is protected by an acetyl group. Dilute aqueous sodium hydroxide closes the ring by elimination of hydrogen bromide and the acetyl group.



Small R = CO_2H or H.

[a] Fe + KOH. [a′] Heat. [b] Zn dust + NH_4OH, dil. H_2SO_4, Br_2. [b′] NaOH. [c] Fusion with NaOH or $NaNH_2$.

FIG. 3.—Methods for preparation of indoxyl.

The third method, which employs phenylglycine, is the original Heumann process;[107] and the closely related fourth method, which uses phenylglycine-*o*-carboxylic acid,[108] is the basis for the present commercial synthesis. In both cases, the glycine compound is heated with dry caustic alkali at 280 to 290° or, better, at a lower temperature with sodamide. Many modifications, such as the use of a mixture of the alkali with calcium oxide, with other alkaline-earth oxide or alkali cyanides, with calcium carbide, or the employment of fusion under diminished pressure or in a paraffin melt, have been employed to temper the drastic conditions.

To use phenylglycine-*o*-carboxylic acid requires a cheap source of anthranilic acid. Naphthalene—in that early period practically a waste product—is a convenient starting point. The first step is an oxidation to phthalic anhydride by sulfuric acid in the presence of mercuric sulfate, the catalytic activity of which was discovered by the famous accident of breaking a thermometer in the reaction mixture.[109] Catalytic aerial oxidation has largely supplanted this means. The remaining steps of imide formation, Hoffmann degradation, and reaction of the anthranilic acid with chloroacetic acid are conventional operations.

---

[105] VORLÄNDER and DRESCHER, *ibid.*, **34**, 1857 (1901).

[106] BAEYER and BLOEM, *ibid.*, **17**, 963 (1884).

[107] HEUMANN, *ibid.*, **23**, 3043 (1890).

[108] D.R.P. 79,409; 137,208; *Chem. Zentr.*, I, 110 (1903); 1, 519, 383 (1907).

Indoxyl is a yellow compound that melts at 85°. It has a fecal odor. The solubility in aqueous alkali and the red color with ferric chloride solution suggest that it has some phenolic properties.

The chemical reactions[105] are in general those predicted for such a compound. Nitrous acid forms N-nitrosoindoxyl. Acetic anhydride gives the N-acetyl derivative at ordinary temperatures, the O-acetyl product in aqueous alkali, and the O-N-diacetyl compounds in the presence of sodium acetate at higher temperatures. Bromine converts it to tribromoaniline, as if it were an amino compound with a labile carbonyl group. Sodium amalgam, or zinc dust and warm alkali, reduces it to indole.[104] Benzenediazonium chloride gives 2-phenylazoindoxyl.

The reactions that make indoxyl so interesting are those which involve condensations through the active methylene group. The simplest of these are the reactions with aldehydes and ketones, whereby compounds[110] known as "indogenides" (page 125) are formed.

$$(C_7H_5NO)CH_2 + OCHR \rightarrow (C_7H_5NO)C{=}CHR$$

The reaction is general. Isatin gives indirubin (see page 137); glyoxal[111] and hydrochloric acid form a diindoxyl product,

$$(C_7H_5NO)C{=}CHCH{=}C(C_7H_5NO).$$

Condensation can also occur between the two methylene groups of indoxyl itself through the agency of an oxidizing agent such as hydrogen peroxide, ferric chloride, or air. The product is, of course, indigo. Unlike thioindoxyl, this reaction does not take place by preliminary oxidation of one of the methylene groups to a carbonyl function; for that process would produce isatin as an intermediate, and isatin, as mentioned above, combines with indoxyl to give indirubin.

This condensation with another active methylene system can be observed also in some phenol compounds that react as if they had undergone a tautomeric change to a *p*-methylene ketone. Thymol,[112] or α-naphthol, for example, condenses with indoxyl when treated with ferric chloride in acetic acid or when heated in air with 10 per cent sodium hydroxide to form 4-cymol-2-indolindigo and (naphthalene-1)-(indole-2) indolignon, the formulas of which appear, respectively, below.

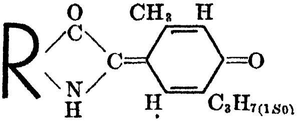
---

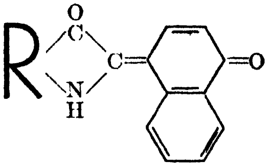
[109] Slosson, "Creative Chemistry," D. Appleton-Century Company, Inc., New York, 1921; Haynes, "This Chemical Age," Alfred A. Knopf, New York, 1942.

[110] Baeyer, *Ber.*, **16**, 2190 (1883).

[111] Friedländer and Risse, *ibid.*, **47**, 1919 (1914).

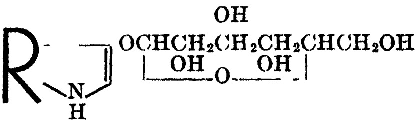
[112] Jolles, *Monatsh.*, **36**, 457 (1915); *J. prakt. Chem.* [2], **92**, 202 (1915).





Proof of these structures is furnished by alkali scission to anthranilic acid and an aldehyde. The aldehyde from the thymol product, for example, is $CH_3(C_3H_7)(OH)C_6H_2CHO$. In the same way, β-naphthol, naphtholsulfonic acid-1,4, and other related compounds condense with indoxyl. The products are named either as substituted indigos or as indolignones.

Indoxyl exists in the indigo plant as a glucoside[113] known as "indican," which was first isolated by the Dutch chemist Schunck. It may be obtained easily by extraction of the stem and leaves with cold acetone. The solution is then concentrated and a yellowish brown viscous material precipitated by petroleum ether. This precipitate is extracted with petroleum ether until no more green colored product is removed. It is then dissolved in water and the solution is decanted to separate solid matter, clarified with ether, decanted to remove tar, treated with a little sodium carbonate to neutralize the plant acids, and finally placed in a vacuum desiccator over sodium hydroxide in order to crystallize. Colorless leaflets, which melt at 57 to 58° and have the composition $C_{14}H_{17}O_6N \cdot 3H_2O$, are obtained. Indican is composed of indoxyl and dextrose.

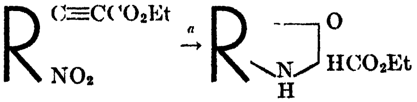


The quantity of indoxyl can be determined easily from an aqueous solution of indican and *p*-nitrobenzaldehyde heated to boiling in the absence of air and treated with hydrochloric acid to precipitate the red crystalline indogenide. Isatin similarly gives indirubin in quantitative yield. When indican is obtained from the plant, an enzyme, indimulsin, is present and effects hydrolysis.

Indoxylic acid and its ethyl ester are intermediates in Baeyer's[104] synthesis of indigo. The ester (m.p. 120 to 121°) is obtained by reduction of ethyl *o*-nitrophenylpropiolate with ammonium sulfide.

---

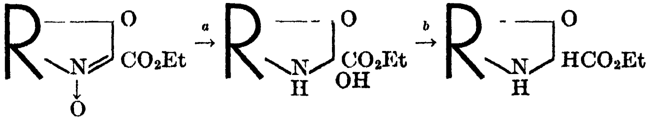
[113] Perkin and Bloxam, *J. Chem. Soc.*, **91**, 1715 (1907); Perkin and Thomas, *ibid.*, **95**, 793, 824 (1909); Thomas, Bloxam, and Perkin, *ibid.*, **95**, 824 (1909).



[a] $(NH_4)_2S$.

The ester contains an unusually reactive hydrogen atom between the carbonyl and carbethoxy groups. The compound is therefore soluble in aqueous sodium hydroxide from which solution it is precipitated by carbon dioxide. It is convertible to a crystalline acetyl derivative by acetic anhydride and to an ethyl ether by ethyl iodide and the potassium or sodium salt. Sulfuric acid sulfonates it. Indoxylic acid loses carbon dioxide at unusually low temperature (see page 122). The ease with which carbon dioxide is lost makes it possible to use this acid—and the ester—in condensations in place of indoxyl itself. Nitrous acid and ethyl indoxylate, for example, give the α-monoxime of isatin.

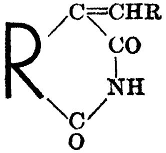
Ethyl isatogenate is isomeric with ethyl *o*-nitrophenylpropiolate, from which it is obtained by solution in cold concentrated sulfuric acid.[104] The structure[114] is probably that of an amine oxide. Reduction by ammonium sulfide converts it to ethyl indoxanthine carboxylate; further reduction by zinc and acetic acid converts it to ethyl indoxylate (see also page 139).



[a] $(NH_4)_2S$. [b] Zn + HOAc or HI.

Indogenides and Isoindogenides.—These compounds have already been mentioned (pages 121, 123) as the condensation products of indoxyl and oxindole, respectively, with benzaldehyde, piperonal, protocatechualdehyde, nitrobenzaldehyde, and other aldehydes. The physical properties of many of these compounds are shown in Table I.

The preparation of such compounds is general and can be observed wherever a similar combination of groups is present. Homophthalimide, for example, has a system—$ArCH_2C(O)NH$— like that present in oxindole. The products of its condensation with aldehydes are known as "isocarbimidindogenides[115] because of the analogy with isoindogenides.



---

[114] Ruggli and Bolliger, *Helv. Chim. Acta*, **4**, 626 (1921); Ruggli, Schmid, and Zimmermann, *ibid.*, **17**, 1328 (1934).

[115] Meyer, *IX Congr. intern. quim. pura applicata*, **4**, 383 (1934); *C.A.*, **30**, 2962 (1936).

Table I.—Indogenides and Isoindogenides

Aldehyde	Indogenide[a]			Isoindogenide[b]		
	M.p., °C.	Color	Ref.	M.p., °C.	Color	Ref.
Benzaldehyde	175–176[c]	Yellow	110	175–176	Yellow	101
Anisaldehyde	....	....	....	155	Yellow	113
Nitrobenzaldehyde	273–274[d]	Red	110, 113	255–257[e]	Yellow-orange	113
o-Dimethylamino benzaldehyde	....	....	....	194–195	Orange	113
o-Hydroxybenzaldehyde	....	....	...	195	Yellow	113
m-Hydroxybenzaldehyde	....	....	....	280	Yellow	113
p-Hydroxybenzaldehyde	....	....	....	280	Yellow	113
Piperonal	217–219	Orange	101	228–229	Yellow	113
Vanillin	....	....	...	224	Yellow	113
Protocatechualdehyde	264–265	Orange-red	101	246	Yellow	113
Resorcinaldehyde	....	....	....	300	Yellow	113
Pyruvic acid	197	Dark red				
Terephthaldehyde	....	Red	110, 111			
Anthroxanaldehyde	....	Red	110			

[a] Usual condensing agent is hydrochloric acid.
[b] Usual condensing agent is piperidine in alcohol.
[c] Heat employed as condensing agent.
[d] The p-isomer.
[e] The m-isomer.

Dioxindole, or 3-hydroxyoxindole, (m.p. 180°) is prepared by reduction of isatin or isatide with 5 per cent sodium amalgam[116] in water or with dilute hydrochloric acid and zinc dust.[117] Further reduction by zinc and stronger hydrochloric acid or by sodium amalgam in weak acid solution gives oxindole.[117] The compound decomposes when heated and at 180° gives aniline. Phosphorus penta- and oxy-chloride mixture gives 2,3-dichloroxindole.

Isatin is used in very many condensations, syntheses, and tests. It was first formed by oxidation of indigo with chromic[118] or nitric[119] acid and may be obtained by similar oxidation of any oxygenated indole such as oxindole, indoxyl, or dioxindole. The best method for synthesis is that of Sandmeyer[120] by cyclization with sulfuric acid (a form of Beckmann rearrangement) of the isonitrosoacetanilide, prepared from aniline, hydroxylamine, and chloral hydrate with hydrochloric acid and sodium sulfate.

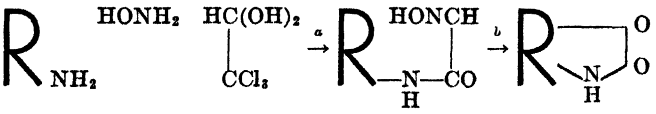
---

[116] Knop, *J. prakt. Chem.* [1], **97**, 65 (1866). See also Ref. 1.

[117] Baeyer, *Ber.*, **12**, 1309 (1879).

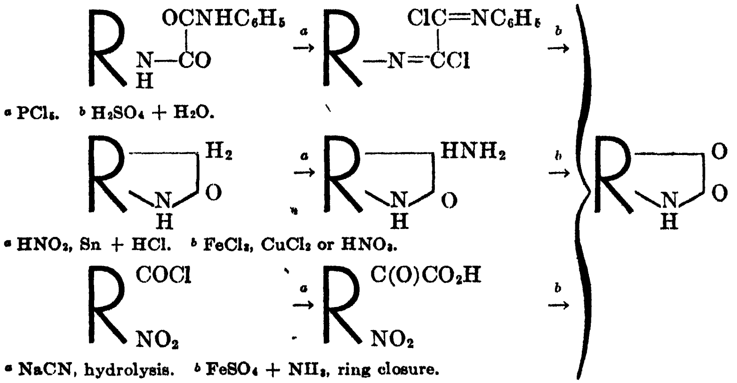
[118] Erdmann, *J. prakt. Chem.* [1], **24**, 1 (1841). For reviews on isatin see Heller, "Uber Isatin, Isatyd, Dioxindol und Indophenin," F. Enke, Stuttgart, 1931. Sumpter, *Chem. Rev.*, **34**, 393 (1944).

[119] Laurent, *ibid.*, **25**, 430 (1842); *Ann. chim. phys.* [3], **3**, 371 (1841).



^{a} HCl + Na_2SO_4. ^{b} H_2SO_4 at 60 to 70°.

Other methods are (*a*) from oxanilides[121] via the dichloroimide $C_6H_4N{=}C(Cl)C(Cl){=}NC_6H_4$, a method that gives poor yields; (*b*) from oxindole[122] by a sequence that gives a nitroso and then an amino intermediate (Baeyer and Knop's synthesis which proved the structure of isatin); and (*c*) by reduction of *o*-nitrophenylglyoxylic acid[123] and ring closure. It may also be isolated from the urine of rabbits that have been fed *o*-nitrophenylglyoxylic acid.[124]



^{a} PCl_5. ^{b} H_2SO_4 + H_2O.

^{a} HNO_2, Sn + HCl. ^{b} $FeCl_3$, $CuCl_2$ or HNO_3.

^{a} NaCN, hydrolysis. ^{b} $FeSO_4$ + NH_3, ring closure.

Isatin melts at 200°, forms yellow-red crystals, and is soluble in hot water, as might be expected from the presence of the two oxygen atoms. It is so feebly basic[125] that it forms a crystalline salt, $(C_8H_5O_2N)HClO_4 \cdot 2H_2O$, with perchloric acid only. N-Methylisatin is, however, a stronger base and dissolves readily in concentrated hydrochloric acid.

The chemistry of isatin may be summarized as being that of (*a*) an active ketone at C_3 that undergoes all the usual reactions of ketones and that condenses with compounds which have an active methylene group or active hydrogen atoms, (*b*) a diketone to a limited extent since the α-carbonyl group is part of an amide system, (*c*) a lactam group that opens readily under the influence of alkali, (*d*) an active hydrogen atom that is responsible for tautomerism and other changes, and (*e*) a bicyclic ring system in which substitution occurs. The molecule presents to a remarkable degree these individual characteristics modified only slightly by their combination as part of a ring.

---

[120] Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919); Marvel and Hiers, *Org. Syntheses, Coll. Vol.* I, 327 (1941); Wibaut and Gearling, *Rec. trav. chim.*, **50**, 41 (1931).

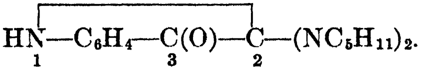
[121] Bauer, *Ber.*, **40**, 2650 (1907); **42**, 2111 (1909).

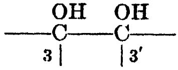
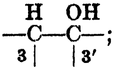
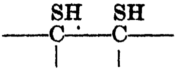
[122] Baeyer, *ibid.*, **11**, 1228 (1878).

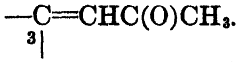
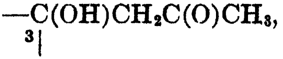
[123] Claisen and Shadwell, *ibid.*, **12**, 350 (1879).

[124] Böhm, *Z. physiol. Chem.*, **265**, 210 (1940).

[125] Hofmann, *Ber.*, **43**, 1082 (1910).

Practically all the familiar ketone properties are found in isatin. Hydrazine hydrate, phenylhydrazine, and hydroxylamine give the β-hydrazone, phenylhydrazone, and oxime, respectively. Hydrogen cyanide forms the β-cyanohydrin. Ammonia in boiling absolute alcohol gives the imino compound,[126] sometimes called "imisatin." Ethyl amine forms the β-ethylimide, and aniline the anil. Piperidine, however, condenses with the α-carbonyl group and gives the dipiperidino compound,[127]  $H\underset{1}{N}\text{—}C_6H_4\text{—}\underset{3}{C}(O)\text{—}\underset{2}{C}\text{—}(NC_5H_{11})_2$.

Reducing agents give the products expected from a ketone. For example, zinc and acetic or dilute sulfuric acid cause bimolecular reduction, as in pinacone formation, to the so-called isatide,[128]  $\text{—}\underset{3|}{\overset{OH}{C}}\text{—}\underset{|3'}{\overset{OH}{C}}\text{—}$; zinc dust and boiling acetic anhydride reduce isatin to tetraacetylisatide[128] in which the two hydroxyl and two imino groups are acetylated; ammonium sulfide links the C_3 atoms of two molecules to form isatan,[116]  $\text{—}\underset{3|}{\overset{H}{C}}\text{—}\underset{|3'}{\overset{OH}{C}}\text{—}$; and hydrogen sulfide in boiling alcohol gives the dithioisatide,[118,119]  $\text{—}\underset{|}{\overset{SH}{C}}\text{—}\underset{|}{\overset{SH}{C}}\text{—}$. Zinc and dilute hydrochloric acid, however, give the monomolecular product dioxindole.

Condensation reactions, characteristic of this active carbonyl group, have been mentioned already under isoindigotin and indirubin (page 123). Isatin also condenses with acetone under the influence of hydrochloric acid to give 3-acetonylideneoxindole,  $\text{—}\underset{3|}{C}\text{=}CHC(O)CH_3$. The reaction can be made to go stepwise,[129] via 3-acetonyl-3-hydroxyoxindole,  $\text{—}\underset{3|}{C}(OH)CH_2C(O)CH_3$, by use of diethylaniline, piperidine, or ammonia as the first catalyst, and then concluded with acid as the second agent. Another molecule of isatin can, similarly, condense with the acetonylideneoxindole. Since these reactions occur with N-methyl isatin, the NH group of isatin plays no part in these condensations.[130] Hydantoin (page 458) also contains an active methylene group that condenses with isatin.

---

[126] Reissert and Hoppmann, *ibid.*, **57**, 972 (1924).

[127] Binz and Huerter, *ibid.*, **48**, 1038 (1915).

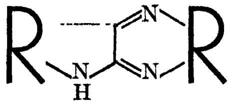
[128] Kohn and Klein, *Monatsh.*, **33**, 929 (1912).

[129] Hill, Schultze, and Lindwall, *J. Am. Chem. Soc.*, **52**, 769 (1930); Braude and Lindwall, *ibid.*, **55**, 325 (1933).

Condensations can occur with the active hydrogen atom of aromatic compounds as illustrated by the formation of 3,3-bis(4-hydroxyphenyl)oxindole—more commonly known as "phenolisatin," $\underset{3|}{—C}=(C_6H_4OH)_2$, from phenol, isatin, and sulfuric acid. The product (m.p. 270°) is similar to phenolphthalein, not only in chemical structure, but also in its mild purgative action,[131] the accompanying irritation from which can be reduced by acetylation. Dimethylaniline forms a similar product[132] with isatin in the presence of zinc chloride. Toluene likewise yields 3,3-di-*p*-tolyloxindole[132] when treated with isatin and concentrated sulfuric acid. Benzene does not so condense.

The condensation with thiophene, known as the "indophenine reaction," is apparently one that involves two active hydrogen atoms per molecule. The result is a product derived from two molecules each of isatin and thiophene, the structure of which has already been discussed (page 46). The reaction with pyrrole leads to a similarly constituted product known as "pyrrole blue."[133]

Evidences of a diketonic function in isatin are not met very often. *o*-Phenylenediamine will, of course, unite in dilute acetic acid to give indoloquinoxaline.[134] Physical measurements, particularly dipole moments,[135] support a diketonic structure. The fact than an α-carbonyl group is a part of an amide system in the ring does not, of course, exclude it from functioning in the manner of a ketone. It is known, for example, that saccharin, which has the amide structure, will also form a phenylhydrazone.[136] The activity of the α-carbonyl group would obviously, however, be much less than that of the β.



As a lactam, isatin undergoes ring opening and forms isatinic acid, $o\text{-}H_2NC_6H_4C(O)CO_2H$, when treated with aqueous caustic alkali. This process may proceed stepwise. Cold potassium hydroxide and isatin produce a violet color, assumed to be caused by formation of N-potassioisatin,[137] which later, when heated or treated with water, changes to the colorless potassium isatinate. Acidification reforms isatin.

---

[130] Hill and Henze, *ibid.*, **46**, 2806 (1924); Hill, Schultze, and Lindwall, *ibid.*, **52**, 769 (1930).

[131] Liebermann and Danaita, *Ber.*, **40**, 3588 (1907); Christensen, *Arch. Pharm. Chemi.*, **88**, 47, 69 (1931); *C.A.*, **25**, 4264 (1931).

[132] Baeyer and Lazarus, *Ber.*, **18**, 2637 (1885).

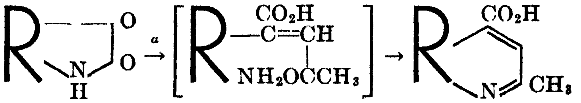
[133] Pratesi and Zanetta, *Atti accad. Lincei*, **22**, 159 (1935); *C.A.*, **30**, 6364 (1936).

[134] Marchlewski, *Ber.*, **28**, 2528 (1895).

[135] Cowley and Partington, *J. Chem. Soc.*, 47 (1936).

[136] Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 596 (1941); *C.A.*, **37**, 100 (1943).

Condensations that occur in the presence of strong alkalies are, accordingly, likely to be accompanied by simultaneous ring opening. If such a condensation has been with acetone, acetophenone, desoxybenzoin, and the like, the opened ring will close again in another position, with formation of a new ring, a quinoline-4-carboxylic acid. The process is known as the "Pfitzinger reaction" (see page 273). The relative velocities of ring opening and condensation may considerably affect the yield of the final cinchonic acid. If the double bond is formed before ring opening is completed, the product is not a cinchonic acid; if adolization has been the only reaction that has occurred, the product, $-\underset{3\,|}{\mathrm{C}}(\mathrm{OH})\mathrm{CH_2COCH_3}$, will undergo the customary ring enlargement when treated with potassium hydroxide.[129]



[a] $CH_3COCH_3 + NaOH$.

The ease with which the amide system in isatin is opened provides a convenient step to some compounds in the aromatic series. For example, 5-iodoisatin, treated with bromine, changes to 5-iodo-7-bromoisatin, and this compound in turn, when treated with 3 per cent hydrogen peroxide, undergoes oxidative cleavage to 2-amino-3-bromo-5-iodobenzoic acid.[138]

The tautomerism of isatin is one of the oldest examples of such phenomena in organic chemistry. Both nitrogen and oxygen derivatives are found. The nitrogen atom, for example, is readily acetylated[139] or benzoylated[140] when heated with acetic anhydride or benzoyl chloride, respectively, and is methylated by use of the sodium salt and methyl iodide[140] or sulfate.[141] If, however, isatin is treated with alcoholic potassium hydroxide and then with silver nitrate and this silver salt is treated with methyl iodide, the O-methyl ether is formed. The structures[142] of the two methyl ethers have been established by synthesis and by chemical reactions. The bright red N-methyl ether (m.p. 134°) can be obtained independently from N-methyl indole and sodium hypobromite or from oxalyl chloride and N-methylaniline followed by treatment with aluminum chloride.[98] Moreover, the compound forms a

---

[137] HELLER and NÖTZEL, *Ber.*, **40**, 1294 (1907). See also Refs. 118, 119.

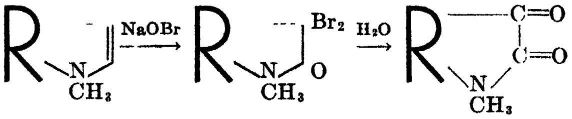
[138] SUMPTER, *J. Am. Chem. Soc.*, **63**, 2027 (1941).

[139] SUIDA, *Ber.*, **11**, 584 (1878).

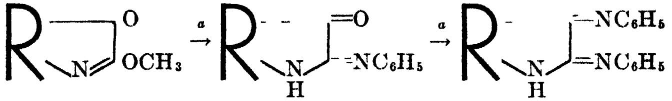
[140] HELLER, *ibid.*, **36**, 2762 (1903); *ibid.*, **40**, 1291 (1907).

[141] BORSCHE and JACOBS, *ibid.*, **47**, 354 (1914).

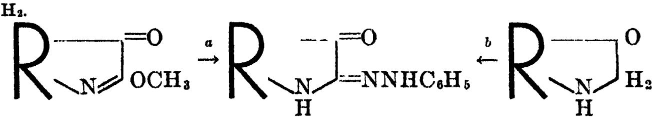
[142] HANTZSCH, *ibid.*, **54**, 122 (1921); **55**, 3180 (1922).



yellow solution of sodium N-methylisatinate when dissolved in alkali and is re-formed unchanged when this solution is acidified. A temperature of 150° causes no change in the properties. A Zeisel determination (HI) gives no methyl iodide. The blood-red O-methyl ether (m.p. 101 to 102°), on the other hand, dissolves slowly in dilute alkali, and the yellow-red solution gives back isatin, not methylisatin, when acidified. Aniline forms first an α-anil, not identical with the β-variety, and subsequently a dianil; phenylhydrazine forms an α-phenylhydrazone identical with that obtained from indoxyl and benzenediazonium chloride.[137] Hydriodic acid gives methyl iodide quantitatively. O-Methyl isatin changes with great ease, even during preparation, to methylisatoid, a yellow bimolecular compound, which melts at 219°, and is a condensation product of the ether with isatin. The isatoid[143] gives no indophenine reaction with thiophene and concentrated sulfuric acid.



[a] $C_6H_5NH_2$.



[a] $C_6H_5NHNH_2$. [b] $C_6H_5N_2Cl$.

Although these chemical tests give definite evidence that a tautomeric condition exists, absorption-spectra studies[144] show no measurable difference between the two ethers, nor for that matter between the ethers and isatin itself.

Chlorine, bromine, nitric acid, or sulfuric acid introduce substituents at C_5.[145] A second group, when it enters the molecule, substitutes at C_7. These positions would be expected since C_5 is para and C_7 is ortho to an amino group, which can be regarded as acylated.

The individual role that these separate parts of the isatin molecule play is emphasized by the fact that other molecules which contain any of these groups will undergo the reactions in question. For example, acenaphthaquinone, benzil, and phenanthraquinone (page 46) can be used in place of isatin[146] in the indophenine reaction; and the keto acids, such as pyruvic acid, and the phthalonic[147] acid behave as does isatinic acid in condensations with active methylene groups.

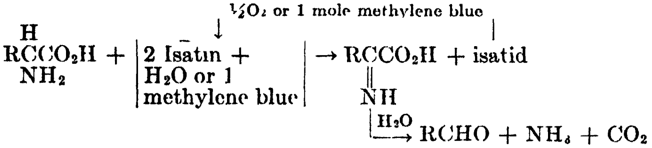
---

[143] Baeyer and Oekonomides, *ibid.*, **15**, 2093 (1882).

[144] Ault, Hirst, and Morton, *J. Chem. Soc.*, 1653 (1935).

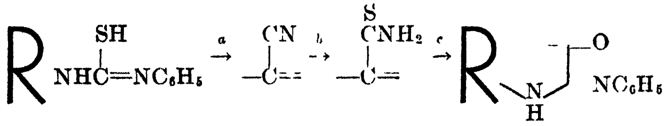
[145] Liebermann and Krauss, *Ber.*, **40**, 2500 (1907).

Isatin and substituted isatins serve as catalysts in the dehydrogenation of amino acids by oxygen or methylene blue. A possible mechanism is suggested[148] by the equation below.



$$\underset{NH_2}{\overset{H}{RCCO_2H}} + \left| \begin{array}{l} 2\text{ Isatin} + \\ H_2O \text{ or } 1 \\ \text{methylene blue} \end{array} \right| \xrightarrow{\tfrac{1}{2}O_2 \text{ or } 1 \text{ mole methylene blue}} \underset{NH}{\overset{}{RCCO_2H}} + \text{isatid} \xrightarrow{H_2O} RCHO + NH_3 + CO_2$$

Isatin-α-anil is produced, as mentioned before, by the reaction of aniline with the O-methyl ether of isatin. Curiously enough, it is not formed with α-chloroisatin.[149] It is obtained also from thiocarbanilide—itself formed from aniline and carbon disulfide—by a succession of treatments with lead cyanide (potassium cyanide and white lead), yellow ammonium sulfide (hydrogen sulfide solution saturated with ammonia and then with sulfur), and concentrated sulfuric acid as shown in the partial formulas below.



^{a} $Pb(CN)_2$. ^{b} $(NH_4)_2S$. ^{c} H_2SO_4 at 90 to 95°. Large R equals C_6H_5 or C_6H_4.

Isatin-α-anil, in contrast to isatin, has an active alpha position. Reduction of an alcoholic solution with freshly prepared ammonium sulfide gives indigo. The compound has also the very interesting property of existing in both the lactam (or anil) and lactim (or anilino) forms. The anil[150] crystallizes as yellowish-brown leaflets from alcohol; the anilino as violet prisms from benzene. Both forms melt at 126°.[149] The corresponding benzoyl derivatives melt at 172 to 173° and 205°, respectively. No indigoid compound is formed from the latter by reduction.

Indigo.—The history of indigo[151a] is long and replete with drama. Mummy cloths show that it was known to the ancient Egyptians; writings in Sanskrit reveal that the Hindus cultivated it. Pliny records that the Romans employed it as a pigment. In the twelfth to fourteenth centuries, certain European dyers began its regular use in Germany, not, however, without considerable opposition from the growers and users of woad, a plant related to indigo, which contains indoxyl combined with another sugar. These interests sought to arouse prejudice by calling indigo a harmful, corrosive "devouring devil" and promoted the passage of laws prohibiting its use. The French also sought to protect the local interest of the woad growers by regulations that required incorporation of woad with indigo in the dyeing operation. The superiority of the latter, however, led to the inevitable evasion and eventual repeal of such restrictions.

---

[146] Candea, *Bull. sci. école polytech. Timisoara*, **8**, 191 (1939); *C.A.*, **33**, 4986 (1939).

[147] Graebe and Trumpy, *Ber.*, **31**, 369 (1898); Kon, Stevenson, and Thorpe, *J. Chem. Soc.*, **121**, 652 (1922).

[148] Langenbeck, *Ber.*, **60**, 930 (1927); **61**, 942 (1928).

[149] Callow and Hope, *J. Chem. Soc.*, 1191 (1929).

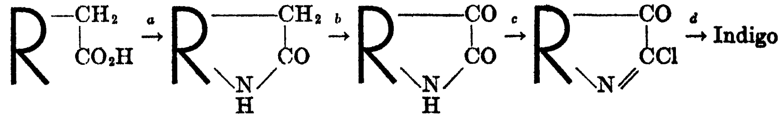
[150] Pummerer, *Ber.*, **44**, 338, 810 (1911).

[151] (*a*) Perkin and Everest, "Natural Organic Coloring Matters," Longmans,

The old method for preparing indigo was to pack freshly cut leaves and stems of the plant, Indigofera (order Leguminosae), in vats under water and allow them to ferment. Indican (page 124) was thus hydrolyzed in about 15 hr. The yellow-orange or olive-green liquid, containing indoxyl, was drawn off. Aerial oxidation precipitated the indigo. The yield varied with the portion of the plant and the season. New leaves contained about 0.7 per cent, old leaves 0.4 per cent. Top leaves had more than bottom ones.

Cultivation of the plant was attempted in many parts of the world but was concentrated in the Dutch East Indies, where the planters acquired a virtual monopoly and enjoyed a high price for their product. The development of synthetic indigo caused abandonment of the plantations. For a brief period during the First World War, when the supply from Germany was cut off, there was a revival of interest in the natural product, only to disappear again permanently[151b] when the war ended and manufacture was established in other countries besides Germany.

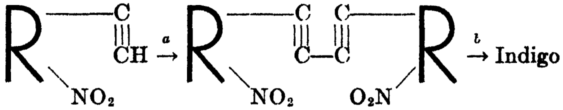
Synthesis of indigo was due to the splendid work of Baeyer. He began with a study of isatin in 1870[53]. In 1878, he prepared indigo from phenylacetic acid via oxindole. Since he had earlier[35] shown that isatin could be converted to indigo by treatment with phosphorus trichloride, phosphorus, and acetyl chloride followed by aerial oxidation, this process can be considered as the first orderly synthesis of the dye. Other and



[a] (1) HNO_3; (2) Sn + HCl or $FeSO_4 + NH_3$; (3) heat. [b] (1) HNO_3; (2) Sn + HCl; (3) $FeCl_3$. [c] PCl_5. [d] Oxygen.

Green and Company, New York, 1918; THORPE and INGOLD, "Synthetic Coloring Matters. Vat Colors," Longmans, Green and Company, New York, 1923; (*b*) DAVIS, *J. Soc. Chem. Ind.*, **43**, 303 (1924).

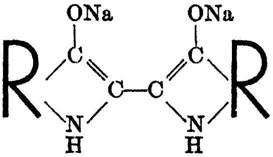
more practical methods quickly followed. *o*-Nitrocinnamic acid was converted to a dibromo compound from which elimination of hydrogen bromide led to *o*-nitrophenylpropiolic acid, which under the reducing influence of glucose and hot alkali changed to indigo. This method, but with sodium xanthogenate and borax as reducing agents for the propiolic acid, proved valuable for calico printing. A synthesis from *o*-nitrophenylacetylene, by which the two parts of the molecule were linked before indigo was formed, was interesting because the diacetylene compound clearly showed that two indole nuclei were joined in indigo.



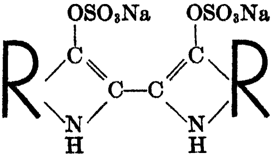
[a] Reaction of *o*-nitrophenylacetylene (obtained from *o*-nitrophenylpropiolic acid in boiling water) with copper followed by potassium ferricyanide. [b] (1) Conc. H_2SO_4; (2) $(NH_4)_2S_x$.

The present practical method of Heumann from anthranilic acid has been described already under indoxyl, which is the primary intermediate.

Indigo is applied to the fiber as a vat dye. The conjugated diketo system $O{=}C{-}C{=}C{-}C{=}O$ is converted by reduction to an alkali-soluble indigo white or dienolic form $HO{-}C{=}C{-}C{=}C{-}OH$. The fiber is dipped in the solution. Aerial oxidation forms the dye on the fiber. The old method of reduction was a fermentation vat that probably contained monosaccharoses. Sodium hydrosulfite, $Na_2S_2O_4$, was subsequently used extensively. In recent years, the reduced form has been stabilized by treatment with the pyridine salt of chlorosulfonic acid, whereby the sodium salt of a half ester of sulfuric acid, known as *indigosol*,[152] is formed. Indigosol is stable to air and, hence, is useful in printing. It is convertible on the fiber to indigo by such a mild oxidizing agent as sodium nitrite.



Indigo white



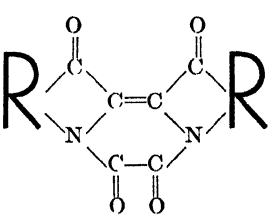
Indigosol

Indigo[153] may exist in a cis or trans form. Derivatives of each are known. For example, oxalyl chloride in boiling nitrobenzene[154] or at

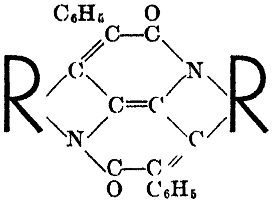
---

[152] Beil, *Z. angew. Chem.*, **37**, 745 (1924); Schultz, *Am. Dyestuff Reptr.*, **23**, 138 (1934).

[153] Indigo is variously referred to as indigo, indigo blue, indigotin, diindogen, bisindol-2-indigo and $\Delta^{2,2'}$-bipseudoindoxyl. The last name is the one employed by *Chemical Abstracts*.

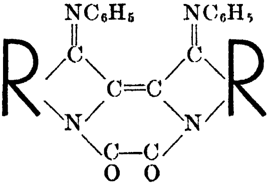


Oxalylindigo



Ciba Lake red B

room temperature,[155] or ethoxyoxalyl chloride,[156] $C_2H_5OC(O)C(O)Cl$, in pyridine for 2 hr., forms the dull yellow *oxalyl indigo* which is a cis derivative. Boiling phenylacetyl chloride[157] gives the red material known as *ciba lake red* B, a trans product. The fact that diacetyl-, dibenzoyl-, and diethoxalyl-indigo are intensely reddish-violet colored compounds suggests that the trans form is the stable variety on the fiber. It does not follow, however, that all cis products are yellow; the dianil of oxalylindigo is violet red. Some tests indicate that the cis form is the one



first deposited on the fiber and that the stable trans isomer forms subsequently.[158] For instance, when a vat is shaken with air at room temperature, the dark blue precipitate first formed is more soluble in organic solvents, particularly in dioxane where this primary and deeper color is stable for a long time. On the other hand, a product prepared at the temperature of the steam bath or one obtained after long standing and drying is not so soluble and has a less intense blue color. Moreover, the more soluble and therefore cis variety dissolves readily in a mixture of 87.5 parts of acetic acid and 12.5 parts of sulfuric acid, whereas the trans form is insoluble.

The hydrolysis of indigo as carried out by Fritzsche[159] with highly concentrated alkali (NaOH or KOH) has considerable historical interest as the first preparation of aniline. The blue color of indigo is destroyed

[154] Friedländer and Lander, *Ber.*, **57**, 648 (1924).

[155] van Alphen, *ibid.*, **72**, 525 (1939).

[156] van Alphen, *Rec. trav. chim.*, **58**, 378 (1939).

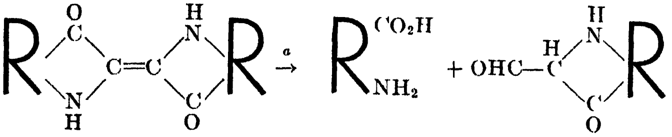
[157] Posner, *Ber.*, **57**, 1799 (1926).

[158] Heller, *Ber.*, **72**, 1858 (1939).

[159] Fritzsche, *J. prakt. Chem.*, I, **20**, 453 (1840); *Ann.*, **36**, 84 (1840).

by the hot alkali and a brown-red mass obtained. Pyrolytic distillation of this brown saltlike product gives ammonia and an oily brown liquid, which by subsequent distillation is obtained colorless. The yield is about 18 to 20 per cent of the indigo used. Fritzsche named this new oil aniline, after the Arabic *an-nil*, which means "the indigo."

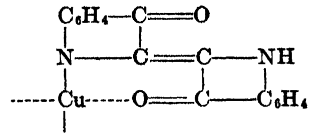
Milder conditions,[160] such as are encountered during the concentration of a dilute alkaline solution until the boiling point reaches 150° give, after acidification, a composition once called chrysanilic acid, which by subsequent heating with dilute mineral acids, particularly sulfuric acid, gives anthranilic acid. Not until nearly 70 years after observation[161] were the processes involved in these reactions understood. As a primary reaction, the alkali promotes a hydrolytic cleavage, possibly stepwise, to indoxyl-2-aldehyde and anthranilic acid.



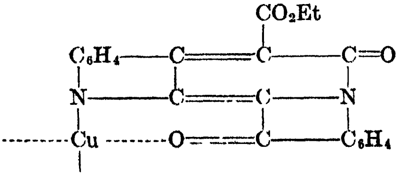
[a] H_2O + NaOH.

As secondary reactions, some of the aldehyde may decompose to indoxyl, and the rest then reacts with this indoxyl, or the aldehyde may condense with the anthranilic acid, or indoxyl may condense with anthranilic acid. A mixture of products results. Moreover, the anil produced with anthranilic acid may later be cleaved by mineral acids. Alkali scission when carried out carefully and for the short time necessary to obtain a maximum amount of cleavage with few by-products is an excellent method for breaking the many kinds of indigo and related molecules into an aldehyde and an acid.

Indigo forms complexes with metals when treated with the metal, or its oxide, carbonate, or acetate in anhydrous high-boiling solvents such as pyridine. The deep black double-refracting crystals of the copper complex, $C_{32}H_{18}O_4N_4Cu$, contain two atoms of active hydrogen (CH_3MgI test) and probably have the structure represented below by a partial formula, in which the primary valencies of the bivalent metal (Cu, Zn)



Indigo-metal complex



Indigomalonic ester-metal complex

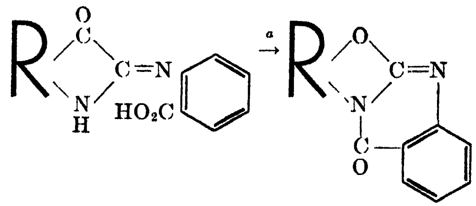
---

[160] Fritzsche, *J. prakt. Chem.* [I], **23**, 67, 79 (1841); *Ann.*, **39**, 76 (1841).

[161] Friedländer and Schwenk, *Ber.*, **43**, 1971 (1910); Friedländer and Kielbasinski, *ibid.*, **44**, 3104 (1911).

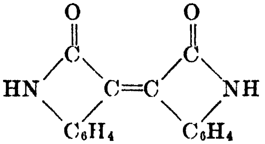
are bound to nitrogen and the coordinated one to oxygen. This formula[162] is supported by the fact that the so-called "indigomalonic ester" forms a beautifully crystalline metal complex also from the reaction of a cold saturated pyridine solution of the ester with a concentrated solution of copper acetate in 22 per cent ammonia.

Oxidation of indigo by air[163] during sublimation, by permanganate,[164] by aerial oxidation of the metal complex in pyridine,[162] or by a concentrated alcoholic solution of silver acetate[165] forms anhydro-α-isatin-anthranilide. Isatin is a probable intermediate. The structure of the yellow compound (m.p. 261°) is proved[166] by subjecting the anil from chloroisatin and anthranilic acid to ring closure by a dehydrating agent such as acetic anhydride or sulfuric-acetic acid mixture.

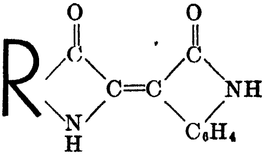


[a] Ac_2O or HOAc + H_2SO_4.

Isoindigo and *indirubin* are isomers of indigo. The former crystallizes from' acetic acid in small brown red crystals (m.p. 350°) and from methanol in plates. The solution in acetic acid is decolorized by zinc dust. The compound[111] is prepared from isatin and oxindole in acetic–hydrochloric acid solution. Indirubin, on the other hand, is prepared from isatin and indoxyl[104] or from chloroisatin and oxindole.[167] Indirubin will form a leuco compound by reduction and act as a vat dye. The reduction, however, is apt to proceed to indoxyl, which on aerial oxidation will give the blue shade of indigo. Decomposition of indirubin



Isoindigo; isoindigotin;
bis-[indol-3-] indigo;
$\Delta^{3,3'}$-dioxindole



Indirubin
Indigo red

---

[162] KUHN and MACHEMER, *ibid.*, **61**, 118 (1928).

[163] PERKIN, *Proc. Chem. Soc. London*, **22**, 198 (1907).

[164] MACHEMER, *ibid.*, **63**, 1341 (1930).

[165] HELLER, *ibid.*, **69**, 563 (1936).

[166] FRIEDLÄNDER and ROSCHDESTWENSKY, *ibid.*, **48**, 1841 (1915).

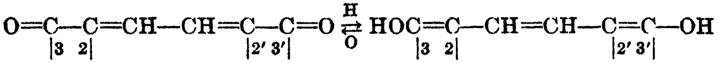
[167] WAHL and BAGARD, *Bull. soc. chim.* [4], **5**, 1043 (1909).

by alkali gives anthranilic acid and oxindole-3-aldehyde[161] analogous to the behavior of indigo.

Bromination of indirubin gives a di- and a tetra-bromo derivative, the last known as ciba heliotrope B[1]. Other substituted indirubins are prepared from substituted isatin, indoxylic acids, or indoxyl.

Bromindigo is the dye that is obtained from the glands of shellfish, *Murex brandaris.* The ancient dyers[151] used this extract in making the famous Tyrian purple. The secretion in the fish is practically colorless. The purple color develops when the fluid or the cloth, stained with the extract of the mollusks, is exposed to sunlight. In 1879, Schunk[168] isolated 7 mg. of crystalline product from 400 mollusks and showed that it had the behavior of a vat dye. Years later, Friedlander[169] allowed the color to develop by exposing the glands of 12,000 specimens of *Murex brandaris* on filter paper to sunlight, mascerated the product with dilute sulfuric acid (1:2), and after filtering and extracting with hot water, extracted the color with alcohol in a Soxhlet extractor. The product, when crystallized from ethyl benzoate and then from quinoline, amounted to 1.4 g. Analysis revealed the composition as $C_{16}H_8Br_2N_2O_2$. Since the color developed from a soluble substance, he reasoned that the colorless compound was probably a molecule with eight carbon atoms and the bromine atom could therefore be in one of four positions on the benzene ring. By comparison with a laboratory preparation, the synthesis of which had been accomplished earlier,[170] he was able to show that the natural product was 6,6′-dibromoindigo. Modern dyes surpass this famous natural one in brilliancy.

Conjugated Indigo Analogues.—When indoxyl is warmed with an aqueous alcoholic acid (HCl) solution of glyoxal bisulfite, a product is obtained[111] in which the two indoxyl nuclei are separated by a conjugated system as shown by the partial formulas below. The compound crystallizes from nitrobenzene or ethyl benzoate as violet-colored quadratic crystals with a metallic sheen. It sublimes, dissolves in cold concentrated sulfuric acid, undergoes sulfonation in warm sulfuric acid, and behaves as a vat dye. The hydrosulfite reduction product is, however, an intense yellow orange color rather than colorless, because of the presence of three conjugated double bonds. Indoxyl can be condensed similarly with ortho- and tere-phthaldehyde.



$$O{=}\underset{|3}{C}{-}\underset{2|}{C}{=}CH{-}CH{=}\underset{|2'}{C}{-}\underset{3'|}{C}{=}O \underset{O}{\overset{H}{\rightleftarrows}} HO\underset{|3}{C}{=}\underset{2|}{C}{-}CH{=}CH{-}\underset{|2'}{C}{=}\underset{3'|}{C}{-}OH$$

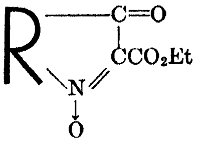
---

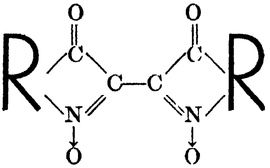
[168] SCHUNK, *J. Chem. Soc.*, **35**, 591 (1879).

[169] FRIEDLANDER, *Monatsh.*, **28**, 991 (1907); *Ber.*, **42**, 765 (1909); *Chem.-Ztg.*, 640 (1911).

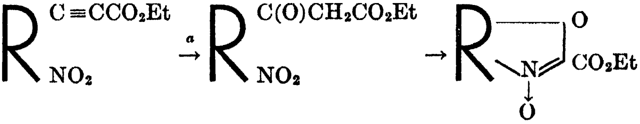
[170] SACHS and KEMP, *Ber.*, **36**, 3303 (1903); SACHS and SECHEL, *ibid.*, **37**, 1868 (1904).

Isatogens were first obtained when Baeyer[171] treated *o*-nitrophenylpropiolate, $NO_2C_6H_4C{\equiv}CCO_2Et$, and *o,ó*-dinitrodiphenylacetylene, $NO_2C_6H_4C{\equiv}CC_6H_4NO_2$, with cold concentrated sulfuric acid. An isatogenate and diisatogen, respectively, isomeric with the original compound, were obtained.

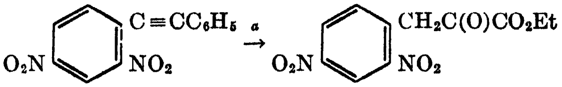

Ethyl isatogenate


Diisatogen

The process depends on proper addition of water to the triple bond and subsequent dehydration of the ketone. Should addition take place in the reverse order, as in the case of 2,4-dinitrotolane, dehydration cannot occur, and the product is a desoxybenzoin. Contrasting cases are shown below.

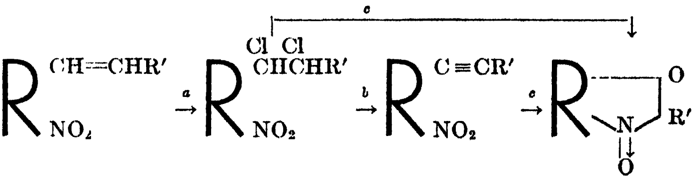


Large R = $C_6H_4<$.
[a] H_2SO_4 aq.



[a] H_2SO_4 aq.

The compounds can be prepared[172] also from pyridine or quinoline solutions of *o*-nitrotolanes or *o*-nitro-*β*-chlorostilbenes by heat or exposure to light. The sequence of reactions from the stilbene compound is shown below.



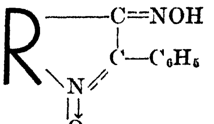
Large R = C_6H_4; small R′ = C_6H_5.
[a] Cl_2. [b] Warm pyridine, KOH. [c] Pyridine and sunlight.

Still another method of preparation[173] is to allow a chloroform solution of an *o*-nitrotolane to stand for many days in the dark with nitrosobenzene. The nitrosobenzene acts as a catalyst.

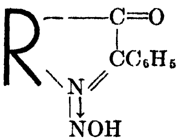
---

[171] BAEYER, *Ber.*, **14**, 1741 (1881); **15**, 50 (1882).
[172] PFEIFFER and COWORKERS, *Ann.*, **411**, 72 (1916).
[173] RUGGLI, CASPAR, and HEGEDUS, *Helv. Chim. Acta*, **20**, 250 (1937).

Isatogens are like diketones.[172] They have a carbonyl and a nitrone system (see page 198). Like quinones, they are colored, liberate iodine from hydriodic acid, and form black crystalline quinhydrones with their reduction products. They form two oximes. The carbon one is identified by reduction with zinc dust in acid to 3-amino-2-phenylindole. The nitrogen one, by the same treatment, gives phenylindoxyl. Both oximes give acetyl derivatives.



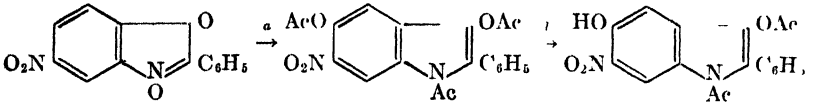
Yellow-orange
(m.p. 236°)



Bright yellow
(m p. 167–168°)

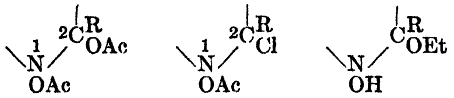
R = C_6H_4.

Acetic anhydride and concentrated sulfuric acid convert the isatogen to a triacetate, after the manner of formation of a triacetate of quinone under the same conditions.[174a] Hot alcoholic hydrochloric acid removes the acetyl group in the aromatic ring; cold sulfuric acid or zinc chloride eliminates all acetyl groups and forms 2-phenyl-5-hydroxy-6-nitro-3-ketoindolenine.



^{a} $Ac_2O + H_2SO_4$. ^{b} Boiling alc. HCl.

Isatogens show 1,3-addition[174b] across the nitrone. Acetic anhydride, acetyl chloride, and cold alcoholic hydrochloric acid give, respectively, the addition products pictured below by partial formulas.

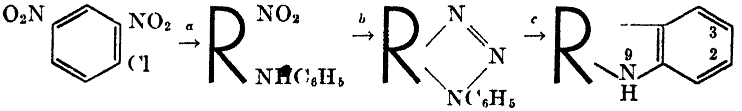


The compounds are called "isatogens" because they were discovered by Baeyer during his work with isatin and other products related to indigo. Baeyer proposed a three-membered ring formula, with the oxygen attached to both nitrogen and the 2-carbon atom. The oxide formula represents better, however, the quinoid character of the compounds. Hot alcoholic hydrochloric acid converts isatogen into isoisatogens,[175] which may have the ring formula suggested by Baeyer. The isatogen is reformed by heating above the melting point for 5 min. or by heating with phenylisocyanate. Reduction of diisatogen with sulfides, with zinc dust and ammonia, or with sugar and warm alkali converts it to indigo.

[174a] Ruggli and Leonhardt, *ibid.*, **7**, 689 (1924). [b] Smith, *Chem. Rev.*, **23**, 193 (1938).

CARBAZOLES

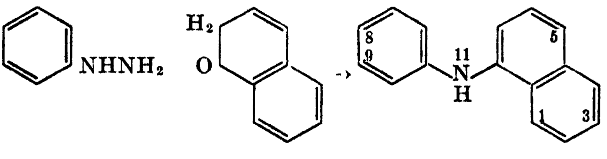
The anthracene fraction of coal-tar contains carbazole, which can be separated by fusion with caustic potash and separation of the potassium carbazole so formed. In the laboratory, the members of this series can be prepared by the Graebe-Williams synthesis, a process that is practically identical with the methods for the preparation of diphenylene oxide. The sequence below shows the steps by which an *o*-aminodiphenylamine is prepared and converted through a triazole to a carbazole.



Large R = $NO_2C_6H_3<$.

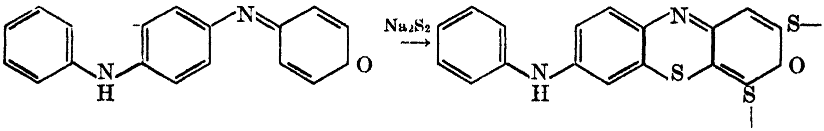
[a] $H_2NC_6H_5$ at 150°. [b] $SnCl_2$ + HCl in HOAc, HNO_2 in HOAc. [c] Decomposition of the triazole at 360 to 380° in an atmosphere of CO_2.

The preparation from phenylhydrazines and α- or β-naphthols by a variety of Fischer indole synthesis has already been mentioned and is illustrated below in the preparation of an 11-benzo[a]carbazole. Similarly, β-naphthol gives 7-benzo[c]carbazole. The numbers 11 and 7 refer to the positions of the nitrogen atom in the two compounds. The letters *a* or *c* refer to the side of the carbazole nucleus to which the benzo group is attached, *a* being the side between C_1 and C_2 of carbazole and *c* the side between C_3 and C_4. A full discussion of naming and numbering is given on page 326.



Carbazole melts at 245° and boils at 355°. It is a feeble base and gives the pine-splinter test as do other pyrroles. Nitrous acid gives an N-nitroso compound that undergoes rearrangement to a 3-nitroso carbazole as in the case of aromatic amines. Nitric acid gives a 3-nitro- and a 3,6-dinitro-product but the stronger warm fuming nitric acid forms 1,3,6,8-tetranitrocarbazole; aqueous sodium or potassium hydroxide and acetyl chloride in acetone solution converts carbazole to an N-acetyl derivative in a manner that parallels the Schotten-Baumann reaction; the Friedel-Craft reaction introduces a benzoyl group at C_3 and C_6 if the nitrogen atom is unsubstituted, but if protected by an acyl or aroyl group, the position taken is at C_2; an N-benzoylcarbazole undergoes rearrangement to a 3-benzoyl product when heated with aluminum chloride at 120°; and sodium and amyl alcohol gives a 1,4-dihydro- and a 1,2,3,4-tetrahydro-compound.[175]

When carbazole is condensed by sulfuric acid with nitrosophenol, an indophenol product results; this product in boiling alcoholic solution with sodium polysulfide yields a dye known as "hydrone blue." The structure is probably that of a thiazine (see page 480).



Carbazole yellow is obtained by tetrazotization of 3,6-diaminocarbazole and coupling with salicylic acid. Polymerized N-vinylcarbazole, sometimes called Luvican, is a product resembling mica.

Problems

1. In each of the following cases suggest a product that is consistent with the reagents employed and the empirical formula given for the product formed: (*a*) Benzoyl-*o*-toluidine heated with sodium ethoxide in a metal bath at 260 to 280.[12] $C_{14}H_{11}N$. (*b*) The *p*-tolylhydrazone of isobutyraldehyde warmed to 60° in alcoholic zinc chloride solution.[176] $C_{11}H_{13}N$. (*c*) *p*-Xylylhydrazine with pyruvic acid followed by heating with zinc chloride.[177] $C_{11}H_{11}NO_2$. (When heated, this compound changes to $C_{10}H_{11}N$, identical with the product obtained from pyrrole and acetonylacetone in acetic acid that contains zinc acetate.) (*d*) Phenylhydrazine and α-ketoglutaric acid, $COOH(CH_2)_2C(O)COOH$, (how prepared?). $C_{11}H_9NO_4$.[178] (*e*) Acetoneanil heated with sodium in ethyl alcohol, until the temperature reaches 105°. $C_{12}H_{17}N$. The product of the reaction of α-naphthylamine with acetone, treated with sodium in boiling amyl alcohol. $C_{16}H_{23}N$.[179] (*f*) α-Naphthyl phenyl amine with oxalyl chloride, followed by treatment with anhydrous aluminum chloride.[98] $C_{18}H_{11}NO_2$. (*g*) N-acetyl-*o*-aminoethylbenzene heated with sodamide.[180] $C_{10}H_{11}N$.

2. Suggest a convenient series of steps for obtaining an indole compound[181] from phenylacetaldehyde.

3. Nitration of 2,3-dimethylindole by nitric acid in concentrated sulfuric acid is suspected of introducing a nitro group in the 5-position. Suggest a synthesis that would confirm such an opinion.[182]

---

[175] Plant and Tomlinson, *J. Chem. Soc.*, 2188 (1922); Plant and Williams, *ibid.*, 1142 (1934); Plant, Rogers, and Williams, *ibid.*, 741 (1935); Stevens and Tucker, *ibid.*, **123**, 2140 (1923).

[176] Grgin, *Monatsh.*, **27**, 731 (1906).

[177] Plancher and Caravaggi, *Atti accad. Lincei*, **14** [V], i, 157 (1905).

[178] Kermack, Perkin, and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

[179] Knoevenagel, *Ber.*, **55**, 2309 (1922).

[180] Keimatsu and Sugasawa, *J. Pharm. Soc. Japan*, **48**, 755 (1928); *C.A.* **23**, 834 (1929).

[181] Weermann, *Ann.*, **401**, 1 (1913); *Rec. trav. chim.*, **29**, 19 (1910).

[182] Plant and Tomlinson, *J. Chem. Soc.*, 955 (1933).

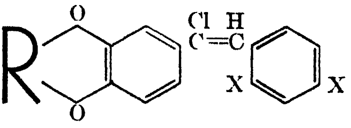
4. Outline the steps for the preparation of 3,3-dimethyl-ψ-indole from ethyl acetoacetate and aniline as starting materials. What reaction is possible if the product is treated with hot mineral acids?[183]

5. What is the product obtained by the following sequence of reactions? An alcoholic solution of *o*-nitrophenylethyl bromide is treated with stannous chloride and hydrochloric acid at 60°; the reaction mixture is cooled, made alkaline by sodium hydroxide and extracted with ether; the residue after evaporation of the ether extract is heated to 150°; and the purified product from these operations is refluxed and stirred in a xylene solution with palladium.[184]

6. Ethyl acetoacetate, 0.5 mole, is heated with two successive portions of benzyl chloride, each 0.5 mole, for 3 hr. each in presence of alcoholic sodium ethoxide. The product is then heated for 2 hr. with hydriodic acid (1.7 sp. gr.) in order to give, in good yield, a compound with the composition $C_{17}H_{18}O$. This material is, in turn, treated first with phenylhydrazine and, subsequently, with zinc chloride for 20 hr. in boiling alcohol, to form a product of the composition $C_{23}H_{21}N \cdot HCl$. What is the probable structure of this compound? When the free base of this last product is treated with acetic anhydride and sodium acetate for 4 hr. at 100°, the product obtained has the composition $C_{25}H_{23}ON$. What is the probable structure?[185]

7. What is the product from the following sequence of reactions which employ the reagents named and produce compounds of the empirical composition indicated?[183] (*a*) *p*-Ethoxyphenylhydrazine condensed with an aldehyde, $O{=}CHCH(CH_3)CH_2CH_2{-}N{-}C_8H_4O_2$ (devise a method for preparing this phthalimido containing compound from aldol), under the influence of hydrochloric acid. $C_{21}H_{20}N_2O_3$. (*b*) Methylsulfate. (*c*) Hydrazine hydrate in absolute alcohol followed by aqueous hydrochloric acid. $C_{14}H_{20}N_2O$.

8. When the compound, pictured below, is dissolved in warm pyridine and exposed to bright sunlight for many days, a product that melts at 282° and has the composition $C_{22}H_{11}N_2O_6$ is obtained in 60 to 65 per cent yield. Suggest a method for obtaining the compound illustrated, and describe all the changes that occur in its transformation to $C_{22}H_{11}N_2O_6$. The reaction of the product with phenylhydrazine at 70° causes nitrogen evolution and formation of a $C_{22}H_{12}N_2O_5$ compound. What is the probable reaction?[186]



R = C_6H_4, X = NO_2

9. 3,4-Dimethoxylbenzaldehyde (how obtained?) is treated with cold concentrated hydrocyanic acid and the product then allowed to react with acetic anhydride and sodium acetate. This compound, $C_{12}H_{13}NO_4$, is dissolved in benzene and ether, and the solution is treated with gaseous hydrochloric acid and then with cold concentrated nitric acid. The product, $C_{10}H_{11}N_2O_5Cl$, is converted by catalytic reduction with hydrogen and palladium in acetic acid to a $C_{10}H_{11}NO_3$ compound, which forms an oxime with hydroxyl amine. What is the probable structure of all products[187] formed?

10. What is the product obtained from the following? (*a*) Chloroacet-*p*-toluide heated with anhydrous aluminum chloride at 230° until evolution of hydrochloric acid ceases.[98] (*b*) *p*-Chloroaniline heated with chloral hydrate and hydroxylamine sulfate and the product of this reaction treated with concentrated sulfuric acid at 60 to 75°.[120] (*c*) *n*-Methylaniline treated with oxalyl chloride and the product allowed to stand many days in carbon disulfide with anhydrous aluminum chloride.[98]

---

[183] ROBINSON and SUGINONE, *ibid.*, 298 (1932).

[184] ADKINS and COONRADT, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

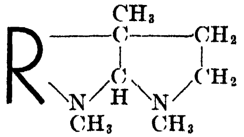
[185] LEUCHS, HELLER, and HOFFMANN, *Ber.*, **62**, 871 (1929).

[186] RUGGLI and DISLER, *Helv. Chim. Acta*, **10**, 938 (1927).

[187] HAHN and SCHULZ, *Ber.*, **72**, 1308 (1939); HAHN and TULUS, *ibid.*, **74**, 500 (1941).

11. *m*-Aminobenzoic acid (how obtained?) is diazotized and treated with ethyl cyclopentanone-2-carboxylate. The orange-brown product is boiled in alcoholic sulfuric acid to which more sulfuric acid is subsequently added. Two isomeric products, $C_{19}H_{23}NO_6$, are obtained.[188] What are the possible structures? What methods might be used to determine the correct structure of each? Name the compounds.

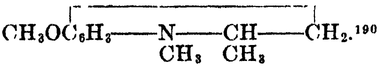
12. Devise a sequence of reactions for the preparation of desoxyeseroline from 1,3-dimethyloxindole.[86]



13. What is the structure of the $C_{22}H_{24}N_2$ compound that results when α-methylindole is heated with isobutyraldehyde?[189]

14. Suggest methods for the preparation of 1-methylindole,[3] 2-methylindole,[51] 3-methylindole,[4] and 1,2-dimethylindole.[189]

15. Suggest a method for the preparation of 1,2-dimethyl-5-methoxyindoline,



$$\overset{\ulcorner\!\!-\!\!-\!\!-\!\!-\!\!-\!\!-\!\!-\!\!-\!\!-\!\!\urcorner}{CH_3OC_6H_3 - \underset{CH_3}{N} - \underset{CH_3}{CH} - CH_2}.$$[190]

16. What is the product from the following sequence of reactions? 1,3-Dimethyloxindole treated with sodium and bromoacetal, the product shaken with 5 per cent hydrochloric acid and then treated with sodium cyanide in the presence of sodium bisulfite to give a compound with the composition $C_{13}H_{14}N_2O_2$. This last product is treated with alcoholic ammonia followed by hydrochloric acid, to give a compound with the composition $C_{13}H_{16}N_2O_3$[102] which, when heated above its melting point (188°) in a vacuum, changes to $C_{12}H_{16}N_2O$.

17. 2-Nitroveratraldehyde, under the influence of acetic anhydride and sodium acetate, condenses with hippuric acid to an azlactone, which has the composition $C_{18}H_{14}O_6N_2$. Hydrolysis with 10 per cent sodium hydroxide for 10 to 15 min. converts this material to an acid with the composition $C_{18}H_{16}O_7N_2$. Prolonged hydrolysis with strong alkali in aqueous ethanol solution, however, causes liberation of ammonia and subsequent formation of orange needles (besides other products) which have the composition $C_{10}H_9O_4N$. This last product forms a semicarbazone, is insoluble in cold aqueous sodium carbonate, but is soluble in aqueous sodium hydroxide, the solution being crimson colored at first, changing to pale yellow in a few minutes. The orange colored material is, however, regenerated by acidification and boiling. Concentrated sulfuric acid dissolves the orange-colored crystals, and this solution becomes green or greenish blue when shaken with thiophene. What reactions[191] take place in this series?

18. What are the products obtained in a synthesis that starts with *o*-nitro-*p*-toluidine and uses each of the reagents listed below in a sequence that ultimately forms a product with the composition $C_{10}H_9NO_2$?[192] (*a*) Sodium nitrite in sulfuric acid. (*b*) Dimethyl sulfate in alkaline solution. (*c*) Ethyl oxalate and potassium ethoxide in anhydrous ether. (*d*) Ferrous sulfate, ammonia, and water. (*e*) Heat (in glycerol). (*f*) Chloroform and potassium hydroxide.

---

[188] Koelsch, *J. Org. Chem.*, **8**, 295 (1943).

[189] Renz and Loew, *Ber.*, **36**, 4326 (1903); Degen, *Ann.*, **236**, 153 (1886).

[190] Späth and Brunner, *Ber.*, **58**, 518 (1925).

[191] Gulland, Robinson, Scott, and Thornley, *J. Chem. Soc.*, 2924 (1929).

19. What product forms in each case below? (*a*) 5-Bromo-1-methyl-oxindole heated with an alcoholic solution of *p*-dimethylaminobenzaldehyde that contains a few drops of piperidine.[98] (*b*) Indoxyl added to an aqueous ethanol solution of 6-aminopiperonal (how prepared?) and the mixture boiled for 4 hr.[191] (Product is $C_{16}H_{10}N_2O_2$.) (*c*) Indoxyl treated with an alcoholic solution of the aldehyde, $C_7H_6O_3$, from pyrocatechol (how prepared?) in the presence of a few drops of piperidine.[191] (*d*) *n*-Phenyloxindole, heated for 2 hr. with moderately strong (1*N*) alkali.[98]

20. Suggest a method for the preparation of an *o*-amino-derivative of malachite green from a heterocyclic compound.[132]

21. The acetyl or benzoyl derivative of isatin might be either N- or O-substituted. What simple test could be made to determine the position?[140]

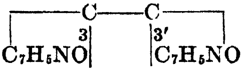
22. Oxidation of the colorless phenolisatin with potassium ferricyanide or with manganese dioxide yields a deep red-violet color which on standing disappears. Suggest an explanation for the appearance of the color.[132]

23. Suggest a method for the preparation of (*a*) Isatin-7-carboxylic acid.[120] (*b*) *n*-Phenylisatin.[98] (*c*) 1-Ethyl-3,3,5-tribromooxindole.[98]

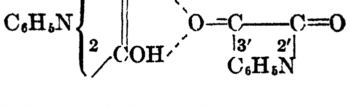
24. Name the product obtained in the following reactions:[98] (*a*) N-Methyloxindole with isatin in the presence of a few drops of hydrochloric acid in acetic acid solution. (*b*) N-Methyloxindole heated with *p*-nitrosodimethylaniline in acetic acid solution. (*c*) N-Ethyloxindole warmed with N-ethylisatin in alcoholic solution with a small amount of piperidine. (*d*) N-Phenylisatin, warmed with *β*-hydroxythionaphthene, in a little alcohol that contains sodium carbonate.

25. What is the product obtained in the following condensations? (*a*) 5-Bromo-*α*-chloroisatin condensed with 3-hydroxythionaphthene.[194] (*b*) Isatin condensed with 3-hydroxythionaphthene.[193,194] (*c*) Isatin-*α*-anilide condensed with 6-methoxycoumaranone.[193] (*d*) Isatin chloride with resorcinol.[193] (*e*) Isatin chloride and *α*- or *β*-naphthol.[193] (*f*) Isatin chloride and *α*-anthrol.[193] (*g*) 5-Chloroisatin-*α*-anilide and 1,8-dihydroxyanthracene.[193] (*h*) Isatin chloride condensed with *α*-hydrindone.[193]

26. The formula of isatide has been the subject of some dispute; one view is that the compound is a pinacone, the other that it is a quinhydrone.



or



Isatide may be prepared from isatin and dioxindole in alcoholic solution in the presence of pyridine. Devise a method for the preparation of 5-methylisatide by two different ways and show what bearing the result might have on the problem of structure.[195]

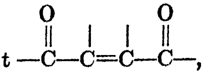
---

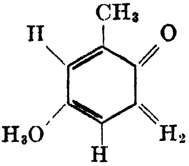
[192] Harvey and Robson, *ibid.*, 97 (1938).

[193] Friedländer, *Monatsh.*, **29,** 359 (1908); **30,** 347 (1909); *Ber.*, **41,** 772 (1908); Bezdzik and Friedländer, *Monatsh.*, **29,** 375 (1908); **30,** 271 (1909); Friedländer and Schuloff, *ibid.*, **29,** 387 (1908); Felix and Friedländer, *ibid.*, **31,** 55 (1910).

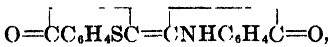
[194] Wahl and Bagard, *Compt. rend.*, **156,** 898 (1913).

[195] Sumpter, *J. Am. Chem. Soc.*, **54,** 2917 (1932); Heller, *J. prakt. Chem.*, **135,** 222 (1932).

27. Many compounds have been prepared which have the unit  $—\overset{\overset{O}{\|}}{C}—\overset{|}{C}=\overset{|}{C}—\overset{\overset{O}{\|}}{C}—$, necessary for a vat dye, yet do not always contain an indole, or for that matter a heterocyclic nucleus. In each of the following instances a colored product is obtained, which, by reduction, yields a colorless or differently colored material from which the original color can be obtained by aerial oxidation. What is the product formed in each case? (*a*) Acenaphthene with potassium dichromate or acenaphthenequinone with hydriodic acid gives an orange-red compound.[196] (*b*) The methyl ether of toluhydroquinone oxidized by dichromate gives a yellowish-red material.[197] (This reaction was known before the structure of indigo was determined.) (*c*) The lactone of *β*-benzoylpropionic acid (how prepared?) treated with ferric chloride in alcohol solution forms a red compound.[198] (*d*) Hydroxythionaphthene, C_8H_6OS, and glyoxal, while dissolved in warm acetic acid that contains a few drops of hydrochloric acid gives an orange-red colored compound that changes to yellow when treated with hydrosulfite.[111] (*e*) Hydroxythionaphthene and maleic di-aldehyde, OHC—CH=CH—CHO, (how prepared?) yields a red-brown compound, $C_{20}H_{12}O_2S_2$, when treated with a few drops of hydrochloric acid in alcohol solution.[111] (*f*) 3-Methyl-6-hydroxybenzoylformic acid condensed with 3-hydroxthionaphthene-2-carboxylic acid in glacial acetic–sulfuric acid solution.[199]



28. Devise a synthesis for 6,6′-dibromoindigo that utilizes a substituted benzaldehyde as the starting material.[170]

29. When 2-thionaphthene-2-indole indigo,  $O=CC_6H_4SC=CNHC_6H_4C=O$, is heated with alkali at 150° and the product then warmed with dilute mineral acid, a crystalline red dyestuff, blue-violet in alkali, is obtained in good yield. The analysis shows the composition $C_{17}H_{10}O_2S_2$.[200] What is the probable structure of this compound? Account for its formation.

30. When an ethanol solution of the acetyl derivative of 3-hydroxy-2,5-diphenylfuran is refluxed with ferric chloride for 3 hr., the product formed has the composition $C_{32}H_{22}O_4$. What is the probable structure of the compound formed? With what system would the product be compared? What would be the probable result of treating the $C_{32}H_{22}O_4$ compound with (*a*) catalytic hydrogen over platinum oxide in a mixture of acetic anhydride, zinc chloride, and concentrated hydrochloric acid; and (*b*) bromine in carbon tetrachloride solution?[201]

31. Terephthaldehyde (how prepared?) is allowed to react with 2,4-dinitrotoluene in the presence of a few drops of piperidine at 160°. The product ($C_{22}H_{14}N_4O_8$) is suspended in acetic acid and treated with chlorine at 110°, and the addition compound, $C_{22}H_{14}N_4O_8Cl_4$, is then boiled in pyridine for 4 hr. to give a compound of the composition $C_{22}H_{12}N_4O_8Cl_2$ (m.p. 248°). This last compound is allowed to stand in a suspension of pyridine for 7 months in sunlight. The color changes slowly from yellow to dark brown. The crystals, when recovered, are violet-brown, melt at 294°, and have the composition $C_{22}H_{10}N_4O_8$. What is the probable structure of the product? When a suspension of this final product in alcohol is warmed on a water bath with phenylhydrazine, nitrogen is evolved and the solution becomes clear. The black powder recovered after addition of water to this solution gives orange-colored crystals ($C_{26}H_{18}N_4O_8$) when heated with acetic anhydride and sodium acetate. Explain the changes.[202]

---

[196] Graebe and Gfeller, *Ann.*, **276,** 17 (1893).
[197] Nietzki, *ibid.*, **215,** 161 (1882).
[198] Kugel, *ibid.*, **299,** 50 (1897); Thiele and Salzberger, *ibid.*, **319,** 196 (1901).
[199] Fries and Finck, *Ber.*, **41,** 4284 (1908).
[200] Friedländer and Kielbasinski, *ibid.*, **44,** 3098 (1911).
[201] Lutz, McGinn, and Bailey, *J. Am. Chem. Soc.*, **65,** 843 (1943).

32. Devise a method for the preparation of gramine, which is β-(dimethylaminomethyl)-indole from indole.[203]

33. Apply the Fischer indole synthesis to the synthesis of a tetrahydro carbazole from cyclohexanone as one component.[175] How would you convert the tetrahydro compound to an unreduced carbazole?

34. How would you prepare 9-aminocarbazole from carbazole? What is the product of the reaction of this amino compound with sodium hypochlorite if its analysis is $C_{24}H_{16}N_4$?[204]

35. N-Alkyl-2-acetylcarbazoles (how prepared?) react with paraformaldehydes and the hydrochlorides of secondary amines, such as dimethylamine, in boiling ethyl or isoamyl alcohol. Reduction of the product over platinum oxide gives $C_{18}H_{22}N_2O$. What reactions have occurred?[205]

36. Devise a method for the preparation of 3,6-dibenzoylcarbazole from nonheterocyclic compounds.[175]

---

[202] RUGGLI and WOLFF, *Helv. Chim. Acta*, **19**, 5 (1936).

[203] WIELAND and HSING, *Ann.*, **526**, 188 (1937); KUHN and STEIN, *Ber.*, **70**, 567 (1937).

[204] WIELAND and SÜSSER, *Ann.*, **392**, 169 (1912).

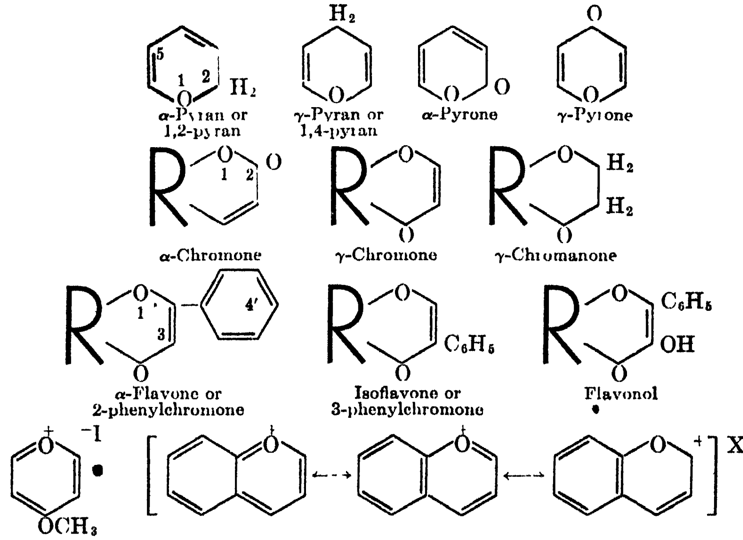
[205] RUBERG and SMALL, *J. Am. Chem. Soc.*, **60**, 1591 (1938).

CHAPTER VII

PYRANS, PYRONES, AND RELATED COMPOUNDS

Six-membered monoheterocyclic rings with an oxygen atom are present in a large number of natural dyes and colored compounds, in vitamin E, in the sweet-smelling constituent of clover, in the hemorrhagic compound in clover, in fish poisons and insecticides, in certain alkaloids, and other substances. In short, the system is widely distributed in nature. Its common occurrence in the root, stem, leaves, and flowers of plants suggests a possible origin from sugars. The chemistry of these substances has been the subject of some famous series of researches.

Naming and Numbering.—The names and numbering system for many members of this class are shown in Fig. 1. The names are largely empirical and related to the source or physical appearance of the compound. For example, pyrone indicates the pyrolytic origin of the compound, chromone the presence of a chromophore that causes color, flavone the yellow appearance, and xanthone (from the Greek word for "yellow") the yellow color of the compound in question. The *one* ending in the above compounds indicates the presence of a carbonyl



α-Pyran or 1,2-pyran

γ-Pyran or 1,4-pyran

α-Pyrone

γ-Pyrone

α-Chromone

γ-Chromone

γ-Chromanone

α-Flavone or 2-phenylchromone

Isoflavone or 3-phenylchromone

Flavonol

γ-Methoxypyrylium iodide

Some resonance forms of a chromylium salt

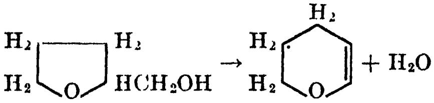
FIG. 1.—Names and formulas of some pyran compounds.

group. The salts obtained by reaction with acids or alkyl iodides are called pyrylium, chromylium, flavylium salts, etc., in order to indicate the resemblance to ammonium and other salts. Chromanone represents the hydrogenated ring system corresponding to chromone. If the hydrogenated ring system contains no carbonyl group, it is known as a chroman. These examples are sufficient to illustrate the general types.

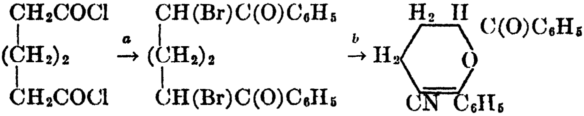
MONOCYCLIC SYSTEMS

Pyrans.—The simplest compounds 1,2- and 1,4-*pyran* are unknown. The tetrahydro-derivatives are anhydrides of diglycols. They can be formed from dibromopentanes by heating with water and zinc oxide at 150°[1] and more slowly with water at 100° in a sealed tube,[2] or from diglycols by treating with 60 per cent sulfuric acid.[3] Pentamethylene oxide is a cyclic ether, which boils at 81 to 82°, and has a density at 0° equal to 0.88. It is less soluble in hot than in cold water. The ring is opened by hot concentrated hydrochloric acid with formation of a mixture of the 1,5-diol and the 1,5-dichloro compounds.

Dihydropyran is prepared by the catalytic dehydration of epoxy-1,4 pentanol-5-(tetrahydrofurfuryl alcohol).[4] In common with other vinyl ethers, it has a very reactive double bond.



Dihydropyrans can be prepared[5] also from derivatives of adipic acids by the following series of steps:



^{a} $C_6H_6 + AlCl_3$, Br in CCl_4. ^{b} NaCN.

Cyclobutane derivatives are obtained if a dibromoester instead of the corresponding diketone is used.

Pyrones.—*α-Pyrone* is obtained by distillation of the mercury salt of coumalic acid[6] and for this reason has sometimes been called "coumalin." It boils at 206 to 209° at 717 mm. with a little decomposition. At 13 mm., it distills at 120°.

---

[1] Clarke, *J. Chem. Soc.*, **101**, 1788 (1912).

[2] Hochstetter, *Monatsh.*, **23**, 107 (1902).

[3] Demjanow, *J. Russ. Phys. Chem. Soc.*, **22**, 389 (1890).

[4] Paul, *Compt. rend.*, **196**, 1409 (1933); *Bull. soc. chim.*, [5] **1**, 971 (1934).

[5] Fuson, Kuykendall, and Wilhelm, *J. Am. Chem. Soc.*, **53**, 4187 (1931).

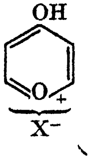
[6] V. Pechmann, *Ann.*, **264**, 303 (1891).

γ-Pyrone is the product of distillation of comenic[7] or chelidonic[8] acid, preferably in the presence of copper powder. It forms hygroscopic needles that melt at 32.5°. The boiling point is 215° (97° at 13 mm.). The ring is opened by alkali to form diformylacetone and by alkali with benzoyl chloride to form the dibenzoate of the enolic form. In the presence of a few drops of concentrated sulfuric acid, ring opening and reaction with ethyl orthoformate occur to give the bisdiethylacetal of diformylacetone. Bromine in the presence of iodine, ferric chloride, or phosphorus gives a yellow perbromide, which undergoes decomposition with steam to give 3-bromo- and 3,5-dibromopyrone.[9] Warm iodine and potassium hydroxide convert it to iodoform. Ammonia at 120 to 140° forms 4-hydroxypyridine.

$$O{=}C(CH{=}CH)_2O + 2C_6H_5COCl + NaOH \rightarrow O{=}C(CH{=}CHO_2CC_6H_5)_2$$

$$O{=}C(CH{=}CH)_2O + HC(OC_2H_5)_3 + H_2SO_4 \rightarrow (C_2H_5O)_2C[CH_2CH(OC_2H_5)_2]_2$$

γ-Pyrone is the parent ring compound of a large number of compounds, for which it plays a role not unlike that of benzene in the aromatic system.[10] For example, it survives pyrolysis when chelidonic, comenic, and meconic acids are heated, a fact that originally suggested the name "Pyrokoman," since shortened to pyrone; it resists the action of ordinary reducing agents in spite of the presence of a carbonyl group that has the appearance of an ordinary ketone; it withstands the action of nitric or sulfuric acid, although it forms pyronium salts readily with such reagents. Such salts are probably responsible for the resistance to nitration and sulfonation, since the presence of a positive pole on a ring makes the system more stable (compare with pyridine).



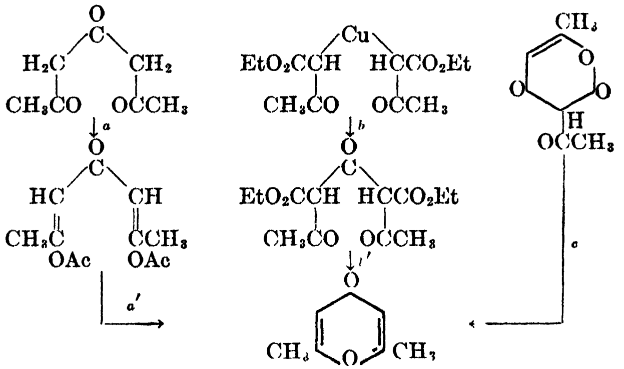
Though a ketone group is present, γ-pyrone forms no hydrazone or oxime derivative.[11] This result, which at first may seem puzzling,[11] is readily understandable, since γ-pyrones combine the properties of a conjugated ring system with those of a lactone. This combination is obvious in the case of α-pyrones; the application to γ-pyrones is equally clear if the molecule is regarded as a lactone with the carbonyl group and oxygen atom doubly connected by vinylogous systems. The easy opening of the ring by alkalies and the re-forming with acids, the failure to form an oxime and hydrazone, and the inability to undergo the reduction common to ketones accord with the view that the carbonyl group in the gamma position is, indeed, of the same type as is present in lactones, further stabilized by resonance of the electrons. The reactions of a ketone are therefore neither expected nor realized.

---

[7] Ost, *J. prakt. Chem.* [2], **29**, 57 (1884).
[8] Willstätter and Pummerer, *Ber.*, **37**, 340 (1904); **38**, 1461 (1905).
[9] Feist and Baum, *ibid.*, **38**, 3569 (1905); Feist, *ibid.*, **40**, 3647 (1907).
[10] Haitinger and Lieben, *Monatsh.*, **6**, 279 (1885).
[11] Collie, *J. Chem. Soc.*, **85**, 974 (1904).

γ-Pyrone forms blue complexes with iodine, similar to those in starch[12] and suggestive of the presence of the cyclic compound in starch.

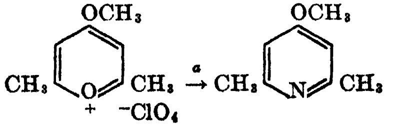
2,6-Dimethylpyrone is made by the methods illustrated in Fig. 2.



[a] NaOEt, CH_3COCl. [a'] Heat in boiling water. [b] $COCl_2$. [b'] Ring closure, saponification, decarboxylation. [c] Hot HCl causes ring opening, ring formation in a new position, and decarboxylation.

FIG. 2.—Preparation of 2,6-dimethylpyrone from diacetylacetone,[11] the copper derivative of ethyl acetoacetate and dehydracetic acid.

It melts at 124° and sublimes easily below 80°. It is very soluble in water and forms salts with acids. Barium hydroxide converts it to diacetylacetone; metallic potassium changes it to a metal ketyl, K—O—C $(CMe{=}CH)_2O$. This pyrone was used in von Baeyer's proof[13] of the structure of the pyronium salts. Treatment with methyl sulfate and then with perchloric acid gives a perchlorate; and this salt, with ammonium carbonate, changes smoothly to 2,6-dimethyl-4-methoxypyridine, the structure of which is unquestioned. Hence the methyl group and the perchlorate ion cannot be attached to the same oxygen atom, and the



[a] $(NH_4)_2CO_3$.

methyl group cannot be attached to the oxygen atom in the ring. The conjugated ring system of three double bonds can, however, provide a structure compatible with all known facts.

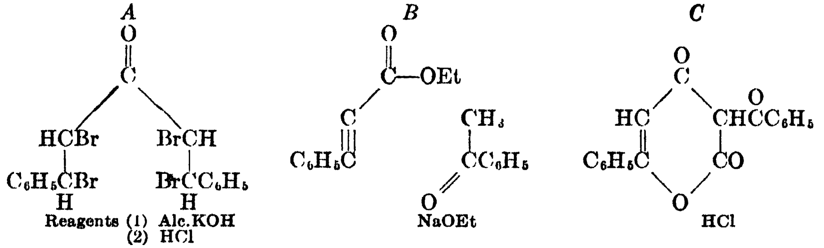
---

[12] BARGER and COWORKERS, *J. Chem. Soc.*, **101**, 1394 (1912); **107**, 411 (1915); **125**, 2407 (1924).

[13] V. BAEYER, *Ber.*, **43**, 2337 (1910).

Phenylcoumalin, or 2-phenyl-α-pyrone, is present in coto bark.[14] It melts at 68°. Sodium amalgam or, better, hydriodic acid at 140° reduces it to δ-phenylvalerianic acid; ammonia converts it to a pyridone; aniline reacts with it to give the product $C_{11}H_5O_2 \cdot 2NH_2C_6H_5$, which in turn with hydrochloric acid gives 1,2-diphenyl-6-pyridone; ammonium acetate in boiling acetic acid changes it to 2-phenyl-6-pyridone, which in turn with zinc dust gives α-phenylpyridine. Phenylcoumalin forms addition compounds with many phenols.

2-6-*Diphenyl-γ-pyrone* melts at 139 to 140° and dissolves in concentrated sulfuric acid but not in boiling hydrochloric acid. Dilute potassium hydroxide does not dissolve it; alcoholic potassium hydroxide resinifies it. The methods of preparation given below are interesting because of their variety and the general principles employed. In *A*, the tetrabromide of dibenzalacetone,[15] suspended in boiling alcohol, is treated with the equivalent amount of alcoholic potassium hydroxide added dropwise. The resulting diethyl ether of the dienol gives the γ-pyrone when heated in a sealed tube with fuming hydrochloric acid. The yield is low. Ethyl chloride and a resinous product result also. In *B*, a Claisen type condensation occurs between the ethyl phenyl propiolate[16] and the active methyl group of acetophenone. A diketone is undoubtedly an intermediate. By the same process, acetone gives 2-methyl-6-phenyl-γ-pyrone. In *C*, the same method used with dehydroacetic acid in preparing 2,6-dimethyl-γ-pyrone is used with dehydrobenzoylacetic acid.[17]



Indalone is the product of the condensation of mesityloxide and dibutyl oxalate under the influence of sodium alkoxide. The compound has attained considerable interest as a mosquito repellent.[18]

---

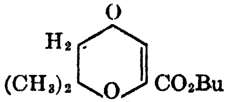
[14] Leben, *ibid.*, **29**, 1673 (1896); Ciamician and Silber, *ibid.*, **29**, 2659 (1896).

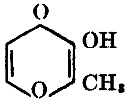
[15] Vorlander and Meyer, *ibid.*, **45**, 3355 (1912).

[16] Ruhemann, *J. Chem. Soc.*, **93**, 432 (1908).

[17] Feist, *Ber.*, **23**, 3726 (1890).

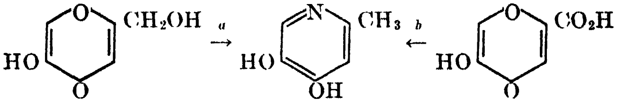
[18] Ford, U.S. patent 2,138,450 (1938); Kilgore, U.S. patent 2,149,917 (1939); *Nat. Geographic*, **85**, 167 (1944).


Indalone


Maltol

Maltol is 3-hydroxy-2-methyl-γ-pyrone[19] (m.p. 159°). It is found in pine needles and larch bark[20] and is formed when barley and certain cereals are roasted in the manufacture of malted beverages. It gives an intense purple color with ferric chloride which sometimes interferes with tests for salicylic acid. Maltol dissolves in potassium hydroxide, reduces silver nitrate and Fehling's solution, decomposes when treated with nitric acid, and forms a mono benzoyl derivative.

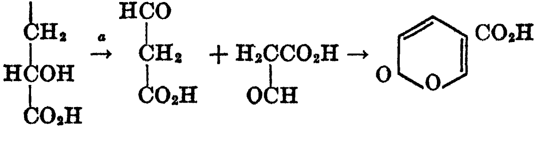
Kojic acid is formed by the action of the fungus *Aspergillus flavus* on xylose and dextrose.[19] Under favorable conditions, the yield is as high as 61 per cent of the sugar consumed. The constitution[21] of Kojic acid is shown by converting it to 4,5-dihydroxy-2-methylpyridine. Since comenic acid is converted to the same compound, Kojic acid must be the alcohol corresponding to comenic acid. The relationship is shown below.


Kojic acid Comenic acid

[a] $(CH_3)_2SO_4$ + KOH forms the dimethoxy product, NH_3 at 100° introduces nitrogen in the ring, HI + P reduces one ether to a methyl group and hydrolyses the other ether group.

[b] NH_3 at 100°, PCl_5 at 150°, Sn + HCl. The last two steps provide a novel way for the conversion of this carboxyl group to a methyl group. The reaction possibly proceeds by way of the intermediate compound, $(HO)_2P(O)O{\cdot}C_5H_2{\cdot}(OH)CCl_3$, that is not isolated.[22] See also page 224.

Pyrone Carboxylic Acids.—Several carboxylic acids of the pyrone series are found in nature or prepared in the laboratory. Coumalic acid is named from malic acid, from which it is derived by the action of sulfuric acid. The first step is the transformation of the hydroxy acid to an aldehyde, a general process for all α-hydroxy acids, and the second step is the condensation of these two aldehydo acids to the α-pyrone derivative. The acid melts at 205 to 210°d.



[a] H_2SO_4.

---

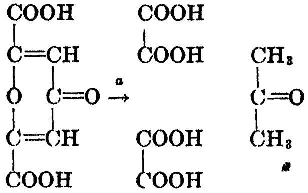
[19] May, Moyer, Wells, and Herrick, *J. Am. Chem. Soc.*, **53**, 774 (1931).

[20] Peratoner and Tamborello, *Ber.*, **36**, 3407 (1903).

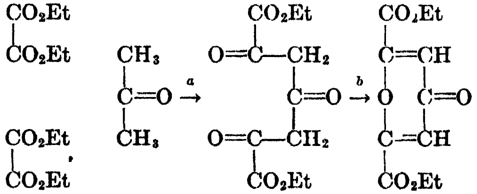
[21] Yubati, *J. Chem. Soc.*, **125**, 575 (1924).

[22] Ost, *Ber.*, **29**, 378 (1884); Ballmann, *J. prakt. Chem.*, [11] **29**, 14 (1884).

Chelidonic acid, 2,6-dicarboxy-1,4-pyrone, occurs in the leaves of the lily of the valley to the extent of about 2 per cent. It was first isolated in 1839 by Probst,[23] who obtained it by extraction of the top and root of *Chelidonium majus,* celandine (a perennial herb of the poppy family, the yellow acrid juice of which was once used internally for jaundice and externally for warts), with warm soda solution and then acidification with strong nitric acid. Its structure was established by decarboxylation[24] to pyrone and by alkaline cleavage to oxalic acid and acetone as pictured below. Its synthesis is accomplished by the method of Ruzicka and Fornasir,[25] which is almost a reversal of the above degradation.

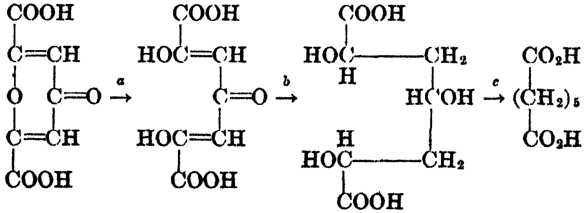


[a] Hydrolysis with alkali.



[a] NaOEt. [b] Conc. HCl.

The alkaline degradation treatment, combined with other reactions, can be made to give a series of products[24] that were of much interest during the period when the structure of this compound was being established. Mild alkaline hydrolysis gives a yellow solution of the salt of an unstable



[a] KOH at ordinary temperatures for a day. [b] NaHg. [c] HI at 200–210° for 10 hr. Chelidonic acid can, of course, be reduced directly to pimelic acid without the necessity of preparing the intermediate xantho- and hydroxantho-chelidonic acids shown here.

FIG. 3.—Degradation products from chelidonic acid.

---

[23] PROBST, *Ann.,* **29,** 113 (1839).

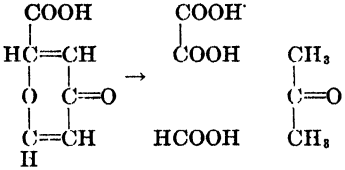
[24] HAITINGER and LIEBEN, *Monatsh.,* **4,** 273, 339 (1883); **5,** 339 (1884); **6,** 279 (1885).

[25] RIEGEL and ZWILGMEYER, *Org. Syntheses, Coll. Vol.* II, 126 (1943).

acid, called xanthochelidonic acid, from which a yellow-red silver salt can be precipitated. The reduction to pimelic acid establishes the presence of a continuous chain of carbon atoms (see Fig. 3).

When dry chelidonic acid is heated with ammonia, it is converted to chelidamic acid by replacement of oxygen by nitrogen.[24]

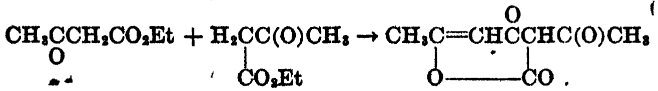
Comanic acid (m.p. 250°d.) is the monocarboxylic acid of γ-pyrone. It can be obtained from chelidonic acid by partial decarboxylation. Caustic alkali causes its decomposition to oxalic acid, formic acid, and acetone.



Meconic acid is 3-hydroxy-γ-pyrone-2,6-dicarboxylic acid. The fact that it is found with the opium alkaloids and that pyrones are converted readily to pyridine compounds is suggestive of a source for some of the alkaloids. Meconic acid is colorless, although it is apt to be yellow from traces of iron.[26] Its triethyl derivative is broken by boiling barium hydroxide solution to ethoxyacetone, ethyl alcohol, and oxalic acid. The acid is synthesized by bromination of acetonedioxalic ester, ring closure, and careful hydrolysis of the bromochelidonic acid product with potassium hydroxide in acetone. Meconic acid probably exists in a colorless keto form and a lemon-yellow enol form. It is considerably more soluble in aqueous boric acid solution than in water alone.

Comenic acid is obtained when meconic acid is boiled with hydrochloric acid (d. = 1.13) until evolution of one equivalent of carbon dioxide ceases. Since the product combines with diazobenzene acetate, a methylene group must be present. Hence the carboxyl group eliminated must come from the position adjacent to the hydroxyl group. Comenic acid is, therefore, 3-hydroxy-γ-pyrone-6-carboxylic acid.[26] Boiling aqueous ammonia converts it to comenanic acid; ferric chloride colors it dark red.

Dehydroacetic Acid.—When ethyl acetoacetate is refluxed with sodium bicarbonate, condensation between the carbethoxy group of one molecule and the active methylene group of another molecule, followed by lactone formation, occurs. An 80 per cent yield of dehydroacetic acid[27] results.



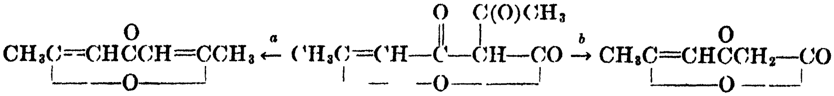
$$\mathrm{CH_3}\underset{\mathrm{O}}{\mathrm{C}}\mathrm{CH_2CO_2Et} + \mathrm{H_2}\underset{\mathrm{CO_2Et}}{\mathrm{C}}\mathrm{C(O)CH_3} \rightarrow \mathrm{CH_3}\underset{\mathrm{O}}{\mathrm{C}}{=}\mathrm{CH}\overset{\mathrm{O}}{\mathrm{C}}\underset{\mathrm{CO}}{\mathrm{CH}}\mathrm{C(O)CH_3}$$

---

[26] VERKADE, *Rec. trav. chim.*, **43**, 879 (1924).

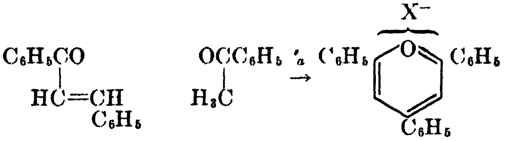
[27] ARNDT, *Org. Syntheses*, **20**, 26 (1940).

Dehydroacetic acid melts at 108°. Boiling hydrochloric acid eliminates carbon dioxide; 90 per cent sulfuric acid eliminates acetic acid.



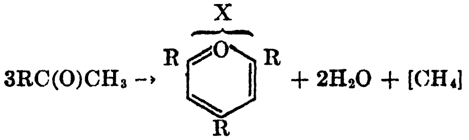
[a] Hot concentrated HCl. [b] 90 per cent H_2SO_4 at 135° for a short time.

Pyrylium Salts.—The reaction of a phenyl styryl ketone and acetophenone with ferric chloride[28] or with boron trifluoride[29] gives a tri-



[a] $FeCl_3$ or BF_3.

phenylpyrylium salt. The same type of compound is produced as a by-product during the preparation of sym-triphenylbenzenes by the action of a mixture of concentrated sulfuric acid and potassium pyrosulfate[30] or of boron trifluoride[29] (potassium borofluoride, boric anhydride, and concentrated sulfuric acid) on acetophenones. A carbon atom is eliminated in this condensation. Methane would be expected as a product. In reality, no evidence of methane, methyl alcohol, formaldehyde, carbon monoxide, or other volatile carbon product has yet



R = C_6H_5, $-C_6H_4OCH_3$.

been observed. The yield of the salt is about as high as that of the triarylbenzene.

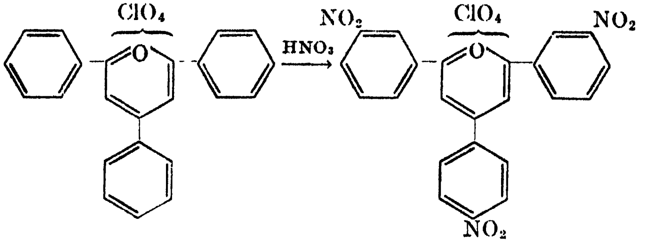
Triarylpyrylium salts are colored. They form picrates and chloroplatinates which have sharp melting points. 2,4,6-Triphenylpyrylium perchlorate can be nitrated by fuming nitric acid.[31] The two phenyl groups nearest to the oxonium pole are nitrated in the meta position; the more remote phenyl group is nitrated in the para position. The yield of this trinitro product is 70 per cent. The positions of nitra-

[28] DILTHEY, *J. prakt. Chem.*, **94**, 53 (1916); **95**, 116 (1917).

[29] DOVEY and ROBINSON, *J. Chem. Soc.*, 1389 (1935).

[30] DAVIS and ARMSTRONG, *J. Am. Chem. Soc.*, **57**, 1583 (1935).

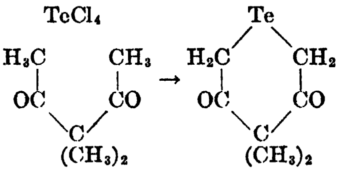
[31] LEFÈVRE and LEFÈVRE, *J. Chem. Soc.*, 2894 (1932).



tion are shown by isolation of *m*-nitrobenzoic acid with a little para acid after permanganate oxidation and by appropriate syntheses and nitrations.

Mild alkaline hydrolysis of the salt with aqueous sodium acetate gives a product that might be regarded as a 2-pyranol.[26] It can be crystallized from benzene-petroleum ether mixture. It adds chlorine or bromine and forms a pyridine compound with boiling alcoholic ammonia. From alcohol containing a little alkali or from pyridine it precipitates with water of crystallization. It also forms a disemicarbazone. These facts suggest that the pyranol may be very similar to, if not identical with, a 1,5 diketone.

Telluro-cyclopentane-3,5-diones.—These compounds resemble in some respects the general form of the pyrones but differ markedly in chemical properties, partly because the carbonyl groups are not ortho and para to the bivalent hetero atom as well as the fact that tellurium is different from the other bivalent hetero atom, oxygen. The compounds are prepared[32] by the reaction of substituted 1,3-diketones with tellurium tetrachloride. The telluro and telluro dichloride compounds result.



The condensation is unique since copper, boron, germanium, tin, zinc, and other metal salts form chelated salts of the enolate form. The telluro compounds form dioximes and hence are diketo compounds. They undergo no ready enolization as shown by the absence of a ferric chloride test. More vigorous treatment disrupts the molecule. Some of the compounds have a powerful antiseptic action in vitro.[33] Telluro-2, 4-dimethyl-cyclo-pentane-3,5-dione is active on *B. coli communis* at concentrations as low as 1 part in 20,000,000; the 2,6-dimethyl isomer is active at 1 part in 10,000,000 to 40,000,000. The action persists in urine but disappears in the presence of serum, because of the colloidal nature of the latter.

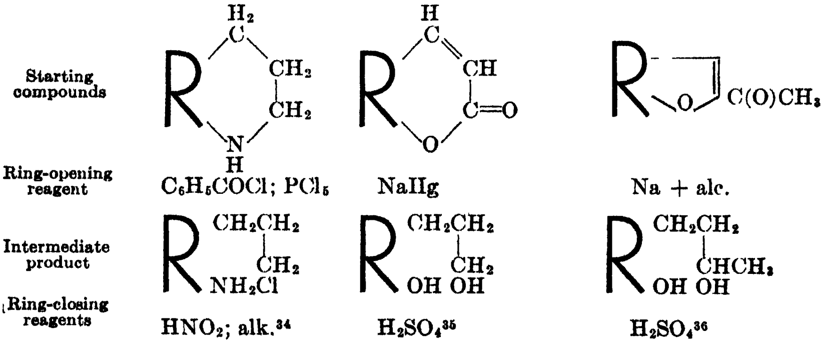
---

[32] Morgan and Thomason, *J. Chem. Soc.*, **121**, 754 (1922); Morgan and Drew, *ibid.*, 735, 1601.

[33] Morgan, Cooper, and Corby, *J. Soc. Chem. Ind.*, **43**, 304 T (1924).

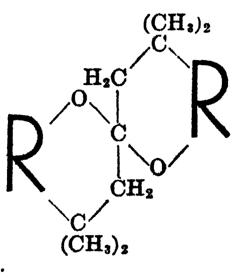
BICYCLIC AND OTHER CONDENSED SYSTEMS

Chromans.—The simplest chromans can be prepared from tetrahydroquinoline by a succession of treatments (C_6H_5COCl, PCl_5, HNO_2, alkali) which constitute an indirect reversal of the formation of piperidine compounds from the oxygen heterocyclic systems. The process involves ring opening and re-formation, as do also the preparations from coumarins and 2-acetylcoumarons. Each of these methods is shown below.



Large R = a benz substituent.

Spirochromans[37] are formed from acetone, *m*-alkylphenols with a free ortho position, and sulfuric acid at 25°. The reaction is probably the result of an intermediate formation of phorone, $[(CH_3)_2C{=}CH]_2C{=}O$, followed by addition of two molecules of the phenol and ring closure.



Large R = C_6H_2R' or $C_6H_2(OH)_2$.

R′ = the alkyl group that is meta to the oxygen atom. The two OH groups are para to the oxygen and carbon respectively.

---

[34] v. Braun and Steindorff, *Ber.*, **38**, 850 (1905).

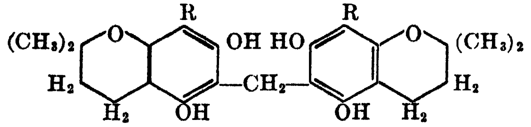
[35] Semmler, *ibid.*, **39**, 2851 (1906).

[36] Stoermer and Schäffer, *ibid.*, **36**, 2863 (1903).

[37] Nierderl and Nagel, *J. Am. Chem. Soc.*, **62**, 324 (1940).

The same type of compound is produced in the condensation of hydroxyquinol with acetone in the presence of acetic and concentrated hydrochloric acid.[38]

Rottlerin[39] is a crystalline constituent of the Indian coloring matter and anthelmintic drug called "kamala," which is obtained from the fruit glands of *Mallotus philippinensis*. The formula has not yet been established but alkaline degradation and hydrogenation give octahydrorottlerone, which has the structure shown below. This compound can be synthesized from the corresponding ketochroman and formaldehyde.

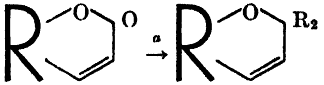


R = $C_6H_5CH_2CH_2C(O)$.

In the unhydrogenated compound R is a cinnamoyl radical.

Other chromans that occur in nature will be mentioned later in this chapter under special headings.

Benzopyrans.—These compounds are labeled either 1,2- or 1,4- (or α and γ) benzopyrans depending on whether the two hydrogen atoms are in the 2- or 4-position. 2,2-Dialkyl-1,2-benzopyrans are obtained by the action of coumarin on excess alkylmagnesium halide. The mechanism of the reaction is not clear. Ring opening has not been shown to occur.[40] The benzopyrone is, however, a cyclic ester, and the Grignard reagent regularly introduces two alkyl groups at the carbon atom of an ester group. Dimethylmagnesium halide gives a 59 per cent and di-*n*-heptylmagnesium a 91 per cent yield. The compounds are interesting because they resemble rings A and B of the deguelin, tephrosin, and toxicarol molecules. In keeping with this relationship, the dimethyl derivative causes paralysis of goldfish within 3 min. The 2,4-dimethyl isomer requires 15 min.



[a] Reaction with 2 RMgX.

Tocopherols.—These substituted chromans are known as Vitamin E. The vitamin affects fertility. The name "tocopherol"[41] is derived from the Greek words tokos and phero, meaning "childbirth" and "bear." The term "tocol" is now employed to indicate the system without alkyl substituents in the aromatic nucleus. α-Tocopherol is, accordingly, 5,7,8-trimethyltocol; β is 5,8-dimethyltocol; and γ is 7,8-dimethyltocol.[42]

---

[38] Baker and Besly, *J. Chem. Soc.*, 195 (1939).

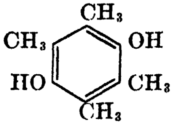
[39] McGookin, Robertson and Tittensor, *ibid.*, 1579, 1587 (1939); McGookin, Percival, and Robertson, *ibid.*, 309 (1938); Backhouse and Robertson, *ibid.*, 1257 (1939).

[40] Shriner and Sharp, *J. Org. Chem.*, **4**, 575 (1939).

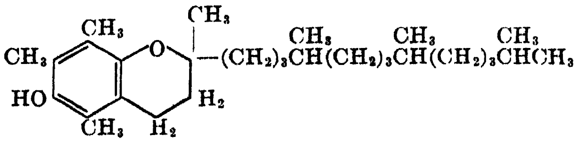
[41] Evans, Emerson and Emerson, *J. Biol. Chem.*, **113**, 319 (1936).

The vitamin was isolated[41] in 1936 from wheat-germ oil by means of a solid derivative formed with cyanic acid. Three allophanates were obtained from the sterol-free concentrate. The one that melts at 158 to 160° was derived from the most potent compound called α-tocopherol, $C_{29}H_{50}O_2$.

Pyrolysis yields durohydroquinone, $C_{10}H_{14}O_2$, in 67 per cent yield. The remaining $C_{19}H_{36}$ fragment is apparently joined to the first by an ether bond but is not eliminated by the ordinary oxidizing agents. Silver nitrate, for example, gives a red oil of approximately the same molecular weight as tocopherol. The duroquinone and the other fractions must therefore be connected at some other point besides the ether link. The compound is either a chroman or a coumaran. Oxidation by chromic acid gives dimethylmaleic anhydride from the aromatic ring, and a lactone $C_{21}H_{40}O_2$ which is a γ or δ lactone because it closes readily. A coumaran ring would give a β-lactone, and the γ-lactone is unlikely because the heterocyclic ring would then be seven membered. A C-methyl determination (oxidation by chromic acid to determine the number of terminal methyl groups in a chain) shows two molecules of acetic acid; and since these values are always low in the case of saturated compounds, there must be at least three methyl branches present. Application of the isoprene rule completes this skillful diagnosis[43] of the structure.



Durohydroquinone

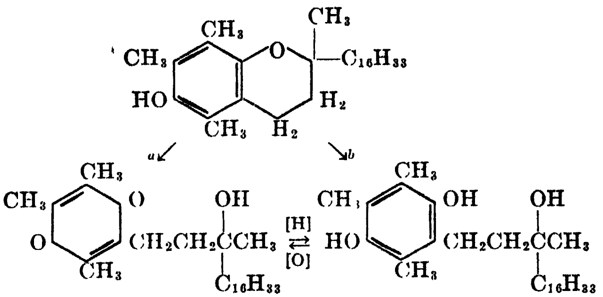


The structure conforms also with the fact that a tertiary carbinol is formed by hydrolysis (opens ring). The hydroquinone is esterified and the carbinol shown to be resistant to esterification and to oxidation by aluminum isopropoxide. The vitamin is synthesized from trimethyl-

[42] Karrer and Fritzsche, *Helv. Chim. Acta*, **21**, 1234 (1934).

[43] Fernholz, *J. Am. Chem. Soc.*, **59**, 1154 (1937); **60**, 700 (1938).

hydroquinone, phytyl bromide, and zinc chloride in ligroin at 60 to 70°.[44]



[a] $AgNO_3$ or $FeCl_3$. [b] HCl.

β-Tocopherol gives trimethylhydroquinone by pyrolysis, *p*-xylenol by reductive cleavage (III), and the same C_{21} lactone as from α-tocopherol by oxidation (CrO_3). One position in the aromatic ring is obviously not filled; and this fact can be proved by the introduction of an allyl group by the reaction with allyl bromide and zinc bromide.[44]

The quantity of tocopherol[45] in the unsaponifiable fraction of wheat-germ oil is 13.4 per cent, in wheat-germ oil is 0.52 per cent, and in wheat germ is 0.0259 per cent. The quantity present in the unsaponifiable fraction of corn-germ oil is 10.2 per cent. Smaller amounts are present in lettuce and other vegetables. The formation of the red-colored quinone by silver nitrate oxidation is an analytical method for analysis of vitamin E.

Coumarins.—The parent of the large class of coumarins is the well-known *coumarin*, a sweet-smelling constituent of clover and the tonka bean. Perkin[46] observed that caustic potash fusion converted this compound to salicylic and acetic acid. He accordingly tried the reaction of salicylaldehyde and acetic anhydride in the presence of sodium acetate (without being aware of the correct structure of coumarin) and thus discovered the famous synthesis that bears his name. He also showed that butyric and valeric anhydrides gave homologues of coumarin.

Coumarin (1,2-benzopyrone) melts at 68° and boils at 302°. It adds chlorine or bromine and subsequently can be converted to coumarone (see Chap. II). Sulfuric and nitric acids introduce substituents at C_6 and to a limited extent at C_8. Phosphorus pentasulfide gives the 2-thio compound. Phenylmagnesium bromide introduces phenyl groups in the 2,- and 4-positions to give 2,4-diphenyl-chromanol-2, probably by ring opening, 1,4-addition, and ring closure.[47] Some 2,2-diphenylchroman is formed also, possibly without ring opening. Sodium bisulfite forms

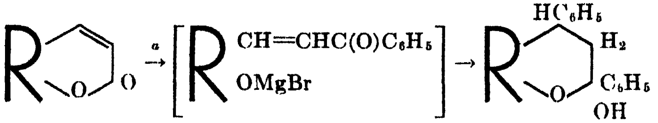
---

[44] Karrer *et al.*, *Helv. Chim. Acta*, **21**, 520, 820, 939, 1234, 1622 (1938).

[45] Smith, *Chem. Rev.*, **27**, 287 (1940).

[46] Perkin, *J. Chem. Soc.*, **6**, 53 (1868).

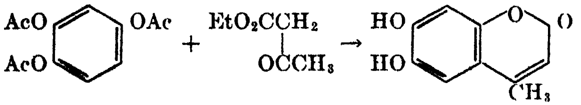
[47] Lowenbeim and Rosenbaum, *Ann.*, **448**, 223 (1926).



ᵃ PhMgBr.

an addition compound with coumarin, possibly by addition across the C_3—C_4 double bond. When the addition compound is warmed with 50 per cent potassium hydroxide, the ring is opened, racemization takes place, and the stable trans *o*-coumaric acid, $HOC_6H_4CH{=}CHCO_2H$, is formed. Mercuric oxide[48] in boiling aqueous solution effects the same change. Sodium amalgam, or zinc dust and alkali, reduces and opens the ring to form melilotic acid, $HOC_6H_4(CH_2)_2COOH$. A bimolecular reduction occurs also in both cases[49] with union at the two C_3, as shown by ring opening and formation of α,α'-bis(2-hydroxybenzyl)-succinic acid.

Umbelliferone, or 7-hydroxycoumarin, is found in nature in the bark of *Daphne mezereum* and in the resins, galbanum and asafetida. In the laboratory, it is prepared from β-resorcylaldehyde, acetic anhydride, and sodium acetate. *Esculetin*, or 6,7-dihydroxycoumarin, is found in the horse-chestnut bark and is prepared in the laboratory from hydroxy-hydroquinone, malic acid, and sulfuric acid.[50] Malic acid in the presence of sulfuric acid becomes an aldehyde acid, which then participates in the condensation. 4-*Methylesculetin*[51] is prepared by a similar condensation between the triacetyl derivative of the trihydroxybenzene and ethyl acetoacetate in the presence of 75 per cent sulfuric acid as shown below.

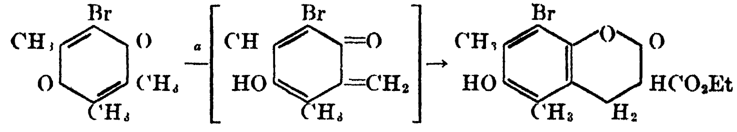


In this preparation of coumarins by v. Pechmann's condensation of phenols with malic acid or ethyl acetoacetate, the presence of hydroxyl, dimethylamino, and alkyl groups, meta to the hydroxy group of the phenol, facilitate the formation of a heterocyclic ring. Nitro and carboxyl groups prevent the condensation, presumably because they inactivate the ring. The *m*- and *p*-chlorophenols give poor yields (3 to 6 per cent). *o*-Chlorophenol gives no coumarin.[52]

---

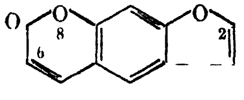
[48] SEN and CHAKRAVATI, *J. Ind. Chem. Soc.*, **7**, 247 (1930).
[49] FRIES and FICKEWIRTH, *Ann.*, **362**, 30 (1908).
[50] v. PECHMANN and KRAFFT, *Ber.*, **34**, 421, 423 (1904).
[51] VLIET, *Org. Syntheses, Coll. Vol.* I, 360 (1941).
[52] CLAYTON, *J. Chem. Soc.*, **93**, 2016 (1908).

5,7-Dimethyl-8-bromo-6-hydroxy-3-carbethoxycoumarin is prepared[53] from durobromoquinone and ethyl sodiomalonate. The condensation is typical of many that employ ethyl acetoacetate and is, moreover, a good example of the influence of various groups. The condensation takes place exclusively at the oxygen atom at the end of the molecule nearest the halogen atom. Enolization in the quinone, followed by 1,4-addition of the sodio compound, is usually regarded as the intermediate step.



[a] $NaCH(CO_2Et)_2$

Furocoumarins.—These compounds, in common with rotenone and deguelin, serve as fish poisons by causing paralysis of the respiratory system. The natives in Java and the East Indies and in South America mascerate the plant and pour the extract on the water. The fish are poisoned, but still fit for human consumption. Peucedanin is reported also as stimulating the alcoholic fermentation of yeast. The structures of several of the compounds are tabulated below as derivatives of the parent furocoumarin.



Peucedanin	2-isopropyl-3-methoxy-
Oreoselone	2-isopropyl-3-hydroxy-[a]
Bergapten	4-methoxy-
Xanthotoxin	9-methoxy-
Imperatorin	9-[3-methylbutenyl-2]oxy-
Alloimperatorin	9-hydroxy-4-[3-methylisobutenyl-2]-

[a] Exists in keto form

The formulas[54] are deduced from examination of the fragments of chemical rupture. Alkali fusion of oreoselone, for instance, gives β-resorcylic acid and that of dihydrooreoselone gives 7-hydroxydihydrocoumarin. Peroxide oxidation of oreoselone gives α-hydroxyisovaleric acid, permanganate oxidation yields 4,6-dihydroxyisophthalic acid and α-hydroxyisobutyric acid, and nitric acid oxidation gives styphnic acid (2,4,6-trinitroresorcinol). These products suggest the formula indicated above. Since peucedanin is converted by hydriodic acid to oreoselone and methyl iodide, the formulas of the two compounds are closely related.

The formula of bergapten is made clear by alkali fusion to give phloroglucinol, and by conversion to a quinone (nitration, reduction, dichromate oxidation). Hence the position that is para to the methoxy group must be unoccupied, and the three rings must have a linear arrangement.

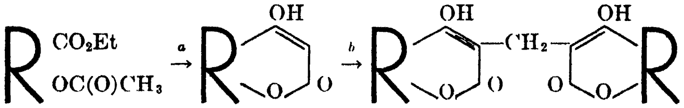
---

[53] Smith and Johnson, *J. Am. Chem. Soc.*, **59**, 673 (1937); Smith and Opie, *ibid.*, **63**, 932 (1941).

[54] Thoms and Baetche, *Ber.*, **45**, 3705 (1912); Späth and Klager, *ibid.*, **66**, 749, 914 (1933); Späth and Holzan, *ibid.*, **68**, 1123 (1935); Späth, *Monatsh.*, **69**, 75 (1936).

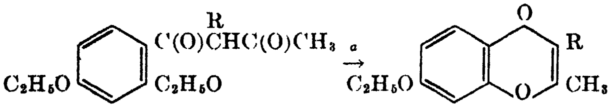
Imperatorin is found in the rhizome of *Imperatoria ostruthium* (masterwort) with several other like compounds, such as hydroxypeucedanin, ostruthol, osthol, ostruthin, osthin, and allo (or iso) imperatorin. Hydrolysis reveals the connection to bergapten.

3,3′-Methylenebis-(4-hydroxycoumarin).—This compound[55] is the active principle present in spoiled hay or silage from the common sweet clover, *Melilotus alba* and *M. officinalis.* Cattle that consume such food acquire the sweet clover disease in which a progressive diminution in the clotting power of blood results. The resultant hemorrhages may be fatal. Synthesis of the compound is outlined below.



[a] Na. [b] H_2CO.

Benzo-γ-pyrones.—Compounds in this series are prepared readily by an intramolecular condensation[56] between an appropriate ketone group and a phenolic group as in the example below.



R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, $CH_2C_6H_5$, etc.

[a] HI. The diketone used in this reaction is made by condensing the diethyl ether of a resacetophenone with ethyl acetate.

The 2-methyl group in this product is conjugated with the carbonyl group and, hence, is sufficiently active to form styryl derivatives readily with aromatic aldehydes.[57] The parallel behavior in the aliphatic series is found with the active methyl group in crotonaldehyde.

FLAVANOLS, FLAVONES, AND RELATED COMPOUNDS

Anthocyanins.—These substituted flavanols are the colored compounds that are responsible for the red, blue, and purple colors of flowers,[58] skins of fruits, and foliage. The name is derived from two Greek words meaning "flower" and "blue." (Cyanin is a common word to indicate a blue color compound, *e.g.*, hydrogen cyanide.) Although the name was applied to these compounds as early as 1835, the chemistry of these pigments dates from 1913 when a crystalline compound was isolated from the blue cornflower.[59]

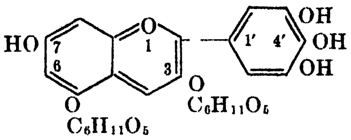
---

[55] Campbell, Roberts, Smith, and Link, *J. Biol. Chem.*, **136**, 47 (1940); Campbell, Stahman, Huebner, and Link, *ibid.*, **138**, 21, 513, 529 (1941); Stahman, Wolff, and Link, *J. Am. Chem. Soc.*, **65**, 2285 (1943).

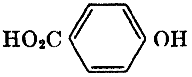
[56] Bloch and Kostanecki, *Ber.*, **33**, 471, 1998 (1900); Kostanecki and Lloyd, *ibid.*, **34**, 2942 (1904).

[57] Zaki and Azzam, *J. Chem. Soc.*, 434 (1943).

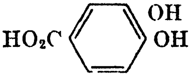
[58] Robinson, *Nature*, **135**, 732 (1935); **137**, 172 (1936); *Proc. Roy. Inst. of Gr. Brit.*, **25**, 21 (1926); *Chemistry & Industry*, 737 (1933); Huntress, *J. Chem. Education*, **5**, 1392 (1928).



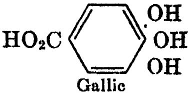
The compounds have one, two, or three hydroxy groups in the phenyl ring and one or two sugar molecules attached to the 3- or 5-positions. The sugar is broken readily from the molecule by means of hydrochloric acid and found to be dextrose, rhamnose, or galactose. The aglucone, called the "anthocyanidin," is then cleaved by fusion with caustic. The products are phloroglucinol (1,3,5-trihydroxybenzene) and one of the three acids shown below depending on whether the anthocyanidin treated is pelargonidin, cyanidin, or delphinidin, respectively.



p-Hydroxybenzoic acid

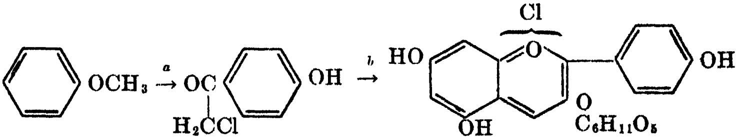


Protocatehuic acid



Gallic acid

Synthesis[60] is accomplished most easily by condensation of a phloroglucinaldehyde with a substituted acetophenone. The steps in preparation of 3-β-glucosidylpelargonidin chloride (callistephin chloride) are shown below.



[a] $ClCH_2C(O)Cl + AlCl_3$ introduces the chloroacetyl group and simultaneously hydrolyzes the ether. [b] KOAc in CH_3CO_2H and EtOH, NaOH, Ac_2O. The product of this sequence of reactions is $HOCH_2C(O)C_6H_4OAc$, which is treated with O-tetraacetylglucosidyl bromide and silver carbonate in order to form $C_6H_7O(OAc)_4OCH_2C(O)C_6H_4OAc$. This product is then treated with 2-benzoyloxy 4,6-dihydroxybenzaldehyde and HCl, after which the acetyl and benzoyl groups are eliminated by alkaline treatment. Acid then forms the colored salts. The condensation between the acetophenone and phloroglucinaldehyde takes place much more smoothly when the phloroglucinol is benzoylated by means of a Schotten-Baumann reaction.

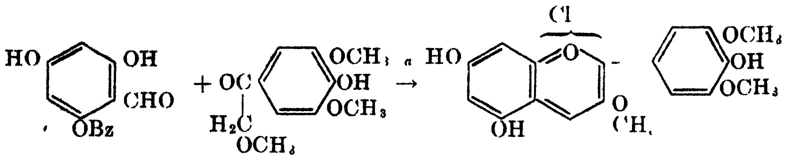
Malvidin chloride[61] may be prepared through an intermediate chalcone, obtained by condensation of a phloroglucinaldehyde with a substituted acetophenone.

---

[59] Willstätter and Everest, *Ann.*, **401**, 189 (1913).

[60] Robertson and Robinson, *J. Chem. Soc.*, 1460 (1928).

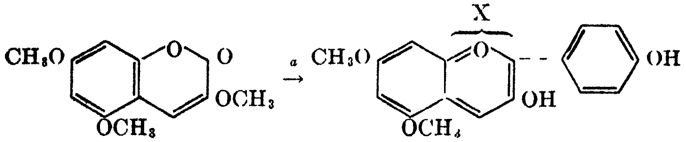
[61] Bradley and Robinson, *ibid.*, 1541 (1928).



3-methylether of malvidin chloride

[a] HCl to cause ring closure, debenzoylation by cold 10 per cent NaOH, HCl to form the salt. The necessary acetophenone is prepared from *o*-acetylsyringoyl chloride and the sodium derivative of ethyl *αγ*-dimethoxyacetoacetate, followed by boiling with aqueous KOH. The dimethoxyacetoacetate is made from ethyl chloroacetate and sodium methoxide in methanol.

The synthesis may be accomplished also by the reaction of a Grignard reagent with a suitable coumarin as illustrated below by one of the early preparations of the dimethyl ether of pelargonidin.[62]



[a] $CH_3OC_6H_4MgX$, H_2O + HX.

Pelargonidin is found as a disaccharide in *Pelargonium zonale*, aster, scarlet salvia, and the rose-colored cornflower. Cyanidin, combined with two molecules of dextrose in cyanin, is about 0.7 per cent of the dry weight of the blue cornflower and 14 per cent of the weight of the dark red variety. Meocyanin is an isomer of cyanin present in the scarlet poppy. Keracyanin is a dirhamnoside of cyanidin present in the sweet cherry. Idaein is a monosaccharide of cyanidin present to about 0.035 per cent in cranberry skins. Asterin and chrysanthemin are cyanidins with one molecule of dextrose. Peonidin is a methyl ether of cyanidin. Delphinidin is present in the larkspur and pansy. Oenin is a monoglucoside of delphinidin present in black grapes. Violanin is a delphinidin with one dextrose and one rhamnose which is present to about 33 per cent in the black pansy. Malvidin is a 3′,5′-dimethoxydelphinidin.

The color of the anthocyanin depends on a number of factors. The more oxygen atoms present, the bluer the pigment. Iron salts intensify the color. The pH of the cell sap and the presence of tannins, organic acids, and enzymes have a profound influence. The presence of anthocyanins is responsible for discoloration of canned fruits and vegetables since the tin dissolved from the container may form complexes of a violet color with the anthocyanin. The anthocyanins are not necessarily derived by reduction from flavones or flavonols, which are yellow pigments, sometimes called anthoxanthins (flower yellow).

---

[62] Willstätter and Zechmeister, *Sitzber. preuss. Akad. Wiss. Physik. Klasse*, 886 (1914); *Chem. Zentr.*, II, 1359, (1914).

The anthocyanins[63] have considerable affinity for wool that has been mordanted with tin, chrome, or alum. The affinity increases in the order perlargonidin, cyanidin, and delphinidin. The colors are not fast to washing.

The anthocyanins are responsible for some of the beautiful red, violet, and blue colors that appear in autumn foliage.[64] An impermeable tissue begins to form between the leaf and the stem, interference with the circulation of cell sap takes place, the sugars manufactured in the leaf are no longer transported to other parts of the plant, the production of the green chlorophyll is retarded, and formation of anthocyanin takes place. Warm sunny days, which permit a maximum amount of sugar formation in the leaf, and cold nights, which interfere with translocation of the cell sap, are best for nature's synthesis of these compounds. An injury to the stem of the leaf will produce the same colors in midsummer. Petals are attached less firmly to the plant than leaves, in accordance with the view that circulation of cell sap should be retarded if colors are to form. The pigments also appear in the early spring before chlorophyll production is at a maximum. The yellow colors in fall foliage are largely due to the presence of flavones. Carotinoids are yellow, red, and brown pigments that are unlike the anthocyanins and flavones in that they coexist with and may modify the green of the chlorophyll during the growing season. Carotins cannot be observed by the eye until the leaf fails to manufacture enough chlorophyll to mask the color of the carotinoid. The final brown color of the foliage is probably caused by oxidation of the flavone salts.

Benzopyrylium Salts.—The question of the structure of the anthocyanidin salts is part of the general problem of chromylium and flavylium salt structure which has been viewed from many interesting and valuable angles. The discussion[65] centers on whether a carbonium or oxonium structure is preferred. A carbonium (Dilthey prefers the term "carbenium" in order to emphasize the tervalent character of the carbon ion) form places the seat of the positive polarity at C_2 or C_4. The arguments for this structure are that (*a*) the reaction with phenylmagnesium halide introduces a phenyl group on a carbon rather than on the oxygen atom; (*b*) peroxide oxidation takes place at C_2, which must therefore be heteropolar and deficient in electrons; (*c*) ozonization[66] of these salts in glacial acetic acid shows decomposition at the $C_2{=}C_3$ and $C_3{=}C_4$ bonds according to the following scheme; and (*d*) an allylic shift between C_2 and C_4

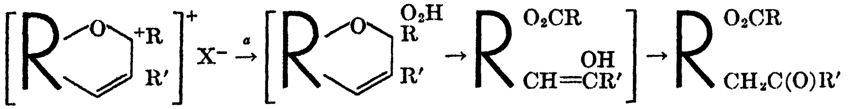
---

[63] PERKIN and EVEREST, "Natural Organic Colouring Matters," Longmans, Green and Company, New York, 1918.

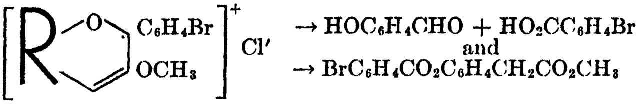
[64] SANDO, *Ind. Eng. Chem., News Ed.*, **9**, 338 (1931); ROBERTS, *Sci. Monthly*, **45**, 427 (1937).

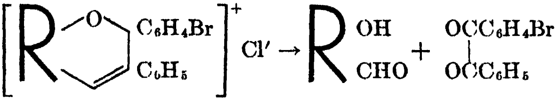
[65] HILL, *Chem. Rev.*, **19**, 27 (1936); HILL and MALHUISH, *J. Chem. Soc.*, 1161 (1935).

[66] SHRINER and MOFFETT, *J. Am. Chem. Soc.*, **62**, 2711 (1940).

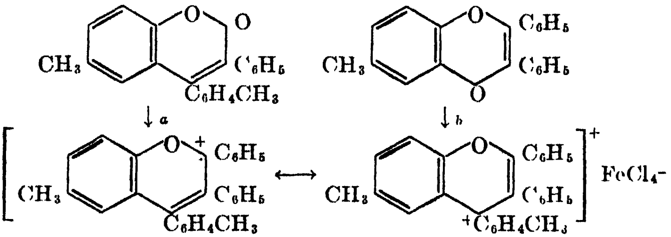


Small R = C_6H_5 R' = H, alkyl or other group.
[a] H_2O_2.



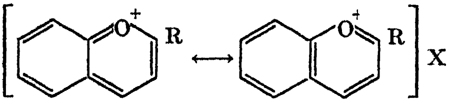


exists as shown by the fact that one product only is obtained in the following examples.

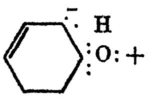


[a] C_6H_5MgBr, $FeCl_3 + HCl$. [b] $CH_3C_6H_4MgBr$, $FeCl_3 + HCl$.

Arguments for an oxonium salt structure are (*a*) that the position in the periodic table suggests that carbon has little tendency to act as a base; (*b*) that the position attacked in the action with the Grignard and oxidizing agents is not a criterion of the original structure of the oxonium ion since neutral tervalent oxygen compounds would not exist and would decompose to give products predicted by the resonance structure below; and (*c*) that any oxygen atom within the ring should add to the stability and resonance of the system. Heats of combustion show that reson-



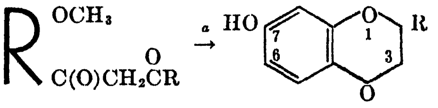
ance[67] is present in phenol itself. It would appear reasonable to assume,



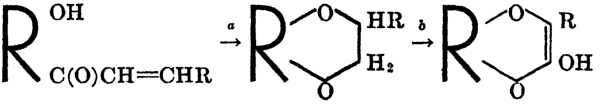
[67] Pauling, Gilman, "Organic Chemistry," Vol. II, John Wiley & Sons, Inc., New York (1938).

therefore, that an atom, whose electrons can resonate with the ring electrons when outside the ring, would be even more able to allow its electrons to so resonate when moved to a more favorable position inside the ring.

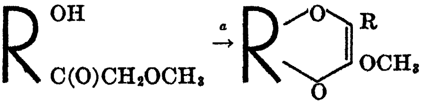
Polyhydroxyflavones.—A large number of these compounds exist in nature combined as glucosides or rhamnosides. They are yellow colored compounds once used extensively as dyes. On cloth, mordanted with chromium, tin, or iron salts, the colors are dark yellow and brown. They are degraded by hot aqueous caustic solution or by fused caustic to resorcinol or phloroglucinol and an aromatic acid as in the case of the anthocyanins. They are synthesized by three general methods outlined below. Large R represents the hydroxylated benz system; small R represents the hydroxylated phenyl ring. Usually the reactions are carried out with the methoxy, rather than the hydroxy, compounds. Hydriodic acid then converts the methoxy to the hydroxy products. The starting material for the first type of condensation is obtained by (*a*) acylation of the ethers of resorcinol or phloroglucinol and (*b*) condensation of the acetophenone with the alkyl benzoate. The chalcones needed for the last two types of synthesis are obtained (*a*) by condensation of resorcin- or phloroglucin-aldehyde, usually as the methyl ether, with appropriate acetophenones, or (*b*) by condensation of an ω-methoxyacetophenone with a benzoic anhydride as in a Perkin condensation. The last two methods are used to introduce a hydroxy group at C_3.



^{a} HI.
R = C_6H_5, C_6H_4OH, $C_6H_3(OH)_2$, etc.



^{a} Hot dil. HCl. ^{b} $C_5H_{11}ONO$, 10 per cent H_2SO_4.



^{a} $(RCO)_2O + RCO_2Na$ + heat.

The names, structure, and melting points of a number of these compounds are tabulated below. Compounds with hydroxy groups in the 3-position are known as flavonols. Flavones can be readily distinguished from flavonols by the resistance of the former to a current of air aspirated through an alkaline solution.

Common name	-hydroxy-flavone	M.p., °C.	Source	Ref.
Chrysin.............	5,7-Di	275	Poplar buds	68
Apiginin.............	5,7,4′-Tri	276–277	*Apium petrolelium* (parsley)	69
Luteolin.............	5,7,3′,4′-Tetra	327	*Reseda luteola* (weld)	63
Fisetin...............	3,7,3′,4′-Tetra	....	Fustic bark	70
Eriodictyol...........	5,7,3′,4′-Tetra	....	Eriodictyon extract	71
Kaempferol...........	3,5,7,4′-Tetra	276–278	Associated with indigo	72
Quercitin.............	3,5,7,3′,4′-Penta	312–314	*Quercus tinctoria*	72
Morin................	3,5,7,2′,4′-Penta	290 d.	*Morus tinctoria*	72
Myricetin............	3,5,7,3′,4′,5′-Hexa	360 d.	*Myrica nagi*	73

The compounds were used mostly for dyes. Luteolin, from weld, is one of the oldest known dyestuffs.[63] It was used by the Gauls in the time of Julius Caesar. Fustic bark and other products have been largely replaced by synthetic dyes. Eriodictyol is one of the components of eriodictyon, an extract from *Eriodictyon californicum*, known commonly as consumptive weed, mountain balm, gum plant. The extract is used as an expectorant and as a bitter principle in medicine. Hesperitin is the 4′-methyl ether of eriodictyol. There is some discussion at present as to whether hesperitin or its water-soluble chalkone has the so-called vitamin P activity that regulates the permeability of the capillaries.

Butein is obtain from the flowers of *Butea frondosa*, which grows in India to a height of 30 to 40 ft. The flowers have a bright orange color and furnish a nonpermanent yellow dye[63,74] which is much used by the natives during the Holi festival season, after which the cloth is washed to its original whiteness. Butein is a tetrahydroxybenzylideneacetophenone (a tetrahydroxy chalkone), and butin is the corresponding flavanone, made from butein by the action of dilute sulfuric acid. Butein and butin exist in the plant as glucosides.

Hesperitin is a cleavage product from hespeidin, a glucoside which is found in citrus fruits.

---

[68] "Merck Index." 5th ed. Merck and Co. Inc. Rahway, N.Y. (1940).

[69] PERKIN, *J. Chem. Soc.*, **71**, 805 (1897); **72**, 666 (1898); CZAJKOWSKI, KOSTANECKI and TAMBOR, *Ber.*, **33**, 1988 (1900).

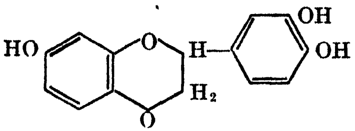
[70] KOSTANECKI and KUGLER, *ibid.*, **37**, 784 (1904); KOSTANECKI and NILKOWSKI, *ibid.*, **38**, 3587 (1905).

[71] KING and ROBERTSON, *J. Chem. Soc.*, 1704 (1931); SHINODA and SATO, *J. Pharm. Soc., Japan*, **49**, 64 (1929).

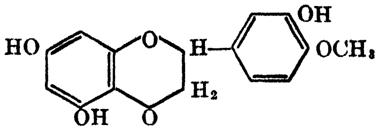
[72] KOSTANECKI, LAMPE, and TAMBOR, *Ber.*, **37**, 1402 (1904); **39**, 625 (1906).

[73] KALFF and ROBINSON, *J. Chem. Soc.*, **121**, 181 (1925).

[74] PERKIN and HUMMEL, *J. Chem. Soc.*, **85**, 1459 (1904); KING and ROBERTSON, *ibid.*, 1704 (1931).

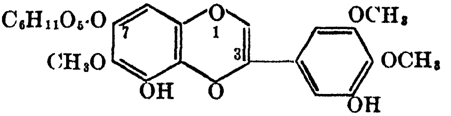


Butin



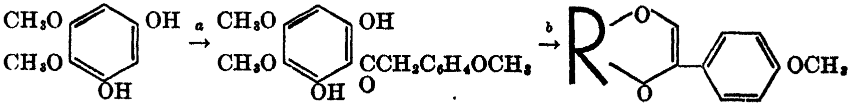
Hesperetin

Isoflavones.—When the aromatic substituent on a chromane system is attached to the beta position the compounds are known as isoflavones. They are less common than the flavones. Iredin (m.p. 208°) is a glucoside, found in the dried rhizome of *Iris florentina L.* (orrisroot). The structure[75] is shown below. Hydrolysis removes the sugar and gives iregenin. Aqueous potassium hydroxide decomposition gives the known 3-hydroxy-4,5-dimethoxyphenylacetic acid, methoxyphloroglucinol, and formic acid. When iregenin is treated with dimethyl sulfate and alkali, all hydroxyl groups are methylated; but when it is treated with methyl iodide and alkali, one hydroxy group is unaffected. The product is,



however, a phenol, gives a color with ferric chloride, and forms an acetyl derivative. The hydroxyl group that is in the most favored position for abnormal properties is at C_5. The abnormal character of one hydroxyl group is shown also by the fact that iregenin forms only a dibenzoyl instead of a tribenzoyl derivative. These tests and confirmatory ones show that the sugar radical must be attached at C_7.

Tectorigenin is the aglucone of tectoridin and is 5,7,4′-trihydroxy-6-methoxyisoflavone. The dimethyl ether of tectorigenin is obtained[76] by the condensation of 4,5-dimethoxyresorcinol with homoanisylnitrile followed by condensation of the resulting ketone with ethyl formate. Ring closure takes place with the hydroxyl in the unhindered position.



Large R = $(CH_3O)_2(OH)C_6H$.

a $CH_3OC_6H_4CH_2CN + ZnCl_2 + HCl, H_2O$. b CH_3O_2CH + Na, HX.

The 4,5-dimethoxyresorcinol reagent is prepared from guaiacol through the intermediate steps of 4,6-dinitroguaicol, 3,5-dinitroveratrole, 3,5-diaminoveratrole, 3,5-dimethoxyresorcinol. The homoanisylnitrile is obtained by the condensation of anisole with formaldehyde and hydrochloric acid in the presence of zinc chloride followed by treatment of the chloromethyl product with sodium cyanide.

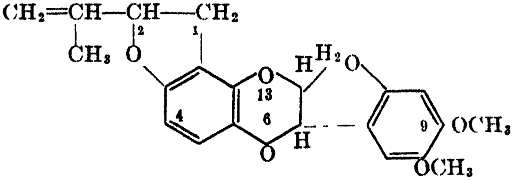
---

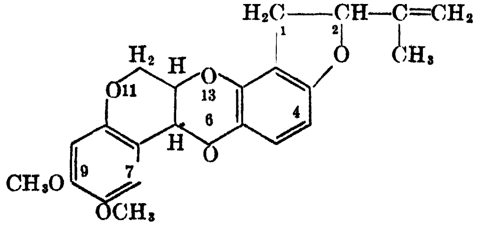
[75] BAKER, *J. Chem. Soc.*, 1022 (1928); BAKER and ROBINSON, **127**, 1981 (1925).

[76] SHRINER and STEPHENSON, *J. Am. Chem. Soc.*, **64**, 2737 (1942).

Rotenone.—The insecticide and fish poison, obtained from the plant Derris of the Fabaceae family and the shrub Lonchocarpus of the Caesalpiniaceae family, which grow in Malaya or the Dutch East Indies and in South America, respectively, is known as rotenone, tubatoxin, or derrin. Large quantities are used in the manufacture of fly and mosquito repellents.[77]

The structure[77] of this compound (m.p. 163°) may be regarded as a hydroxylated and methoxylated isoflavone, to one side of which is fused one isoprene residue to give a dihydrofuran ring, and at the middle of which is a methyleneoxy bridge between two rings. The compound may also be regarded as a chromano-chromanone and also somewhat like an angular furocoumarin but with the carbonyl group in the gamma instead of the alpha position. The formula is written below in two positions, the first to emphasize the isoflavone framework that is present, and the second to accord with the rule for numbering in the "Ring Index." The last arrangement shows a ring sequence much like that in the carcinogenic dibenzanthracene, although the presence of the oxygen atom in the 6-position and other differences are sufficient to eliminate the cancer-producing property of the hydrocarbons.



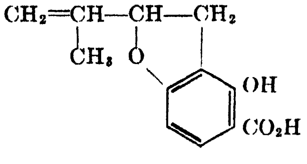


When the customary degradation by strong alkali is applied, the left side of the first molecule above is separated as tubaic acid, which by caustic fusion changes to isotubaic acid. The structure of these two benzofuran products has been discussed already in Chap. II.

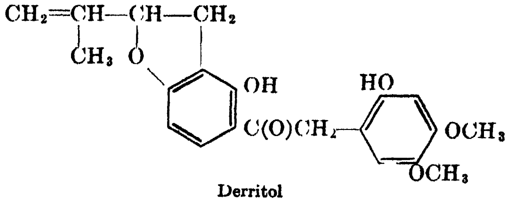
Less drastic alkaline cleavage with simultaneous zinc reduction gives acetaldehyde and derritol, $C_{21}H_{22}O_6$, which by a sequence of methylation,

[77] LaForge, Haller, and Smith, *Chem. Rev.*, **12**, 181 (1933); Haller, *J. Chem. Education*, **19**, 315 (1942); Haller, Goodhue, and Jones, *Chem. Rev.*, **30**, 33 (1942).

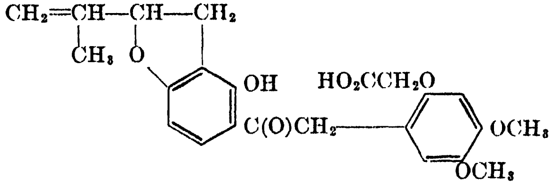
hydrogenation to tetrahydromethylderritol, and oxidation by hydrogen peroxide gives the known trimethoxyphenylacetic acid, a product that comes from the right side of the formula in question.



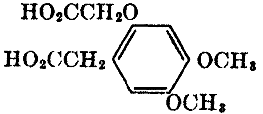
Tubaic acid



Derritol



Derissic acid



Derric acid

Mild alkaline oxidation with iodine eliminates the two hydrogen atoms between the two heterocyclic rings and gives dehydrorotenone. A series of treatments with alcoholic alkali (to give derissic acid), peroxide (to give derric acid), and permanganate oxidation convert dehydrorotenone to rissic acid $(CH_3O)_2C_6H_2(CO_2H)OCH_2COOH$. Decarboxylation of rissic acid gives decarboxyrissic acid, $(CH_3O)_2C_6H_3OCH_2COOH$, which is shown by synthesis to be 3,4-dimethoxyphenoxyacetic acid. Hot acetic anhydride and sodium acetate convert derissic acid to dehydrorotenone.

Strong acids convert rotenone to isorotenone, by rearrangement of the double bond to a position in the furan ring. Catalytic hydrogenation gives dihydrorotenone.

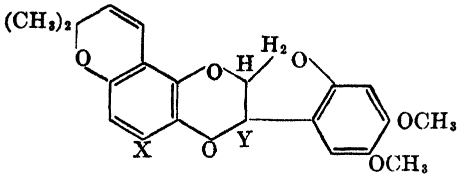
All the above changes, together with numerous tests and supplementary information such as is furnished by hydrazone formation, methoxy determinations, Zerewitinov measurements of active hydrogen, etc., were skillfully explained by Haller and LaForge as characteristic of the formulas given above. The compound has not yet been synthesized, although ring structures of the chromenochromone type have been made.

When the extract from Derris or cube root is concentrated and the rotenone crystals are separated, the residue is found to contain deguelin,[78] tephrosin,[79] and toxicarol,[78] all highly toxic to fish, but much less active

[78] CLARK, *J. Am. Chem. Soc.*, **53**, 313 (1931).

[79] HANRIOT, *Compt. rend.*, **144**, 150 (1907).

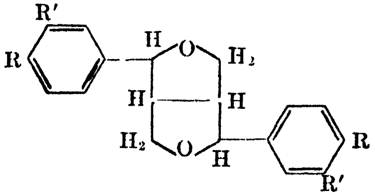
than rotenone.[80] These compounds have a pyran instead of a furan ring, and the last two also have hydroxy substituents. Sumatrol[81] has the same framework as rotenone but has an extra hydroxyl group at C_5. It also is less active than rotenone.



	X	Y	m.p.
Dequelin	H	H	171°
Tephrosin	H	OH	187°
Toxicarol	OH	H	219°

Elliptone has the same structure as isorotenone except for the absence of the isopropyl group in the former. Malaccol has the same structure as elliptone except for the presence of a hydroxyl group at C_5. Apart from the effect of these structural changes, the toxicity of rotenone is decreased[77] 50 per cent by conversion to dihydrorotenone. The acetyl derivatives of the hydroxy compound have less activity, and the hydroxy compounds have still less activity than does rotenone.[80]

The activity of insecticides[82] can often be boosted by the presence of another compound, called a synergist. Rotenone, for instance, is a synergist for pyrethrum. Fused dihydrofuran rings, present in plant materials, have a synergistic effect on the insecticidal action of pyrethrum on houseflies. Over 6½ million pounds of Derris and Lonchocarpus were imported in the United States in 1940 and over 13½ million pounds of pyrethrum.



R of R′ = OH, OCH_3 or RR′ = O_2CH_2.

Dehydrorotenone is a chromenochromone. Compounds of this type may be prepared in the laboratory. One method[83] is shown below. In order to simplify writing the important parts of the formulas, A will be used to designate the methoxy benz end and B the hydroxybenz end of the essential intermediate. The methoxy or hydroxy group is in the meta position to the oxygen atom in the adjacent ring. The synthesis begins

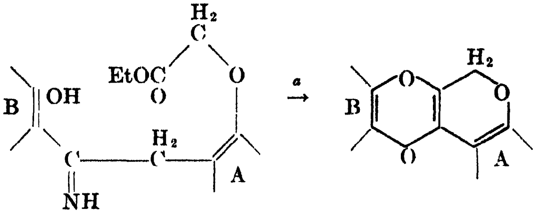
---

[80] Gerbsdorf, *J. Am. Chem. Soc.*, **53**, 1895 (1931); Firik and Haller, *J. Econ. Entomol.*, **29**, 594 (1936).

[81] Robertson and Rusby, *J. Chem. Soc.*, 497 (1937).

[82] Haller, LaForge, and Sullivan, *J. Org. Chem.*, **7**, 185 (1942).

[83] Robertson, *J. Chem. Soc.*, 489 (1933).

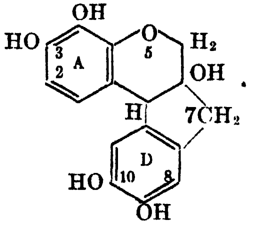


ᵃ Hydrolysis of imino group, double ring closure.

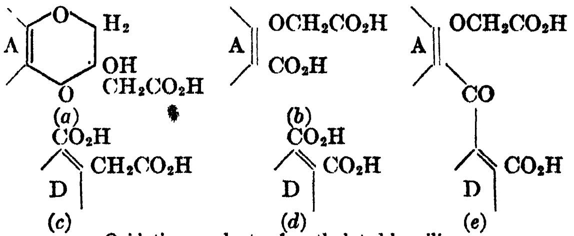
The steps on the A side are (1) to EtO_2CCH_2ORCHO by means of $BrCH_2CO_2Et$, HORCHO, and potassium carbonate in hot acetone; (2) to $HO_2CCH_2ORCH_2C(O)CO_2H$ by means of a condensation of the aldehyde with hippuric acid, acetic anhydride, and sodium acetate followed by hydrolysis with 10 per cent NaOH and then acidification; and (3) to $CH_3O_2CCH_2ORCH_2C{\equiv}N$ by means of hydroxyl amine, followed by dehydration of the oxime with acetic anhydride and then esterification of the acid at the other end of the molecule by CH_2N_2. This nitrile is then condensed with resorcinol by use of zinc chloride in ether saturated with HCl (Hoesch-synthesis) to give the compound shown on the left above. The double ring closure in step *a* is accomplished, after hydrolysis of the imino group occurs, by hot acetic anhydride and sodium acetate. R = phenyl nucleus in the above steps.

with O-methylresorcylaldehyde and includes such standard operations as the formation of an α-keto acid by use of the azlactone, the formation of a nitrile by dehydration of an oxime, and the condensation of a nitrile with a phenolic compound.

Hematoxylin.—This compound can be regarded as a γ-flavanol with a methylene bridge between two of the rings. Brazilin has the same structure save for the absence of a hydroxyl group at C_4. The structure[84] is derived from a consideration of the degradation fragments. The permanganate oxidation products derived from brazilin, which has been trimethylated in order to protect the hydroxyl groups, are brazilic acid, 2-carboxy-5-methoxyphenoxyacetic acid, 2-carboxy-4,5-dimethoxyphenylacetic acid, *m*-hemipinic acid, and brazilinic acid, listed, respectively, as *a*, *b*, *c*, *d*, and *e* below, by partial formulas which preserve the relative positions of rings A and D to each other.



Hematoxylin



Oxidation products of methylated brazilin

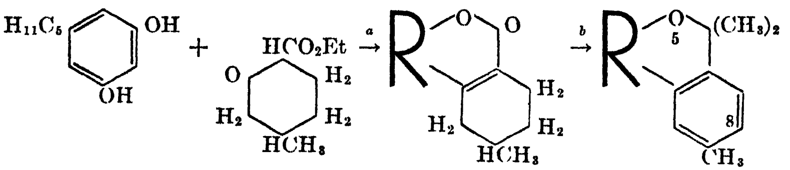
These pieces can be assembled into a structure for brazilin which is supported by the synthesis of brazilinic acid (*e*) by the Friedel-Crafts reaction of the anhydride of *m*-hemipinic acid (*d*) with the ethyl ester of 3-methoxyphenoxyacetic acid, which is the ethyl ester of the acid corresponding to (*b*) less the aromatic carboxyl group. Since hematoxylin by alkali treatment gives pyrogallol, where brazilin gives resorcinol, the structure of these two compounds can be regarded as established. Both products are obtained from brazilwood which was named from *braza* meaning "fiery red." The compounds were once used extensively for dyeing purposes. Hematoxylin is used some as a stain in microscopy and in the manufacture of ink.

---

[84] Perkin and Robinson, *J. Chem. Soc.*, **93**, 489 (1908).

Hematein is obtained from hematoxylin or logwood extract and ammonia by treatment with air. This oxidation converts ring D to a para quinoid structure at C_9.

Cannabinol.—1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran, otherwise known as cannabinol, is isolated, together with the closely related substituted diphenyl compound, known as cannabidiol, from the red oil of *Cannabis indica* and of Minnesota wild hemp. The compound can be synthesized[85] from ethyl 5-methyl-cyclohexanone-2-carboxylate and olivetol (5-*n*-amylresorcinol) by the steps shown below.

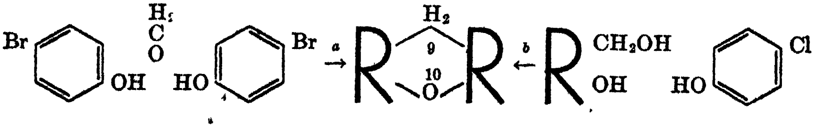


[a] $POCl_3$. [b] (1) $Ac_2O + NaOAc$; (2) S at 225–250°; (3) CH_3MgI.
Large R = $C_5H_{11}(OH)C_6H_2 <$.

Hydrogenation of cannabinol gives a tetrahydro product that has marihuana activity. The relationship between cannabidiol and cannabinol is apparent from the fact that mineral acids and other reagents isomerize the former to a tetrahydro derivative of the latter with loss of one hydroxy group and one double bond. Dehydrogenation with sulfur completes the change to the cannabinol. The compound is probably formed in nature by the condensation of a terpene with olivetol.

XANTHENES, XANTHONES, AND RELATED COMPOUNDS

Xanthenes.—Xanthenes are prepared by condensations of appropriate 2,2′-dihydroxydiphenylmethanes. Two methods[86] of preparation of the parent compound, one from *p*-bromophenol and another from saligenin, are shown below.



[a] H_2SO_4, Na + $C_5H_{11}OH$, heat. [b] HCl, Na + $C_5H_{11}OH$, heat.

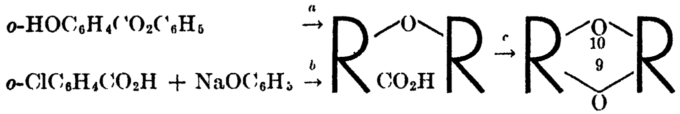
---

[85] Adams and Baker, *J. Am. Chem. Soc.*, **62**, 2401 (1940); Adams, Baker, and Wearn, *ibid.*, 2204.

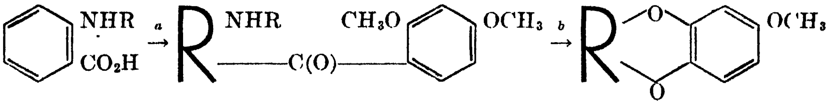
[86] Buehlor, Cooper, and Scrudder, *J. Org. Chem.*, **8**, 316 (1943).

Xanthene melts at 99.5 to 100.5 and boils at 315°. Oxidation converts it to xanthone.

Xanthones.—Xanthones can be prepared (*a*) by the action of sulfuric acid or acetic anhydride on a mixture of salicylic acid and phenol;[87] (*b*) by thermal rearrangement of phenyl salicylate, a process in which phenol is probably formed as an intermediate step; (*c*) by ring closure of a diphenylether-*o*-carboxylic acid,[88] a compound prepared in fine yield from an *o*-chlorobenzoate and a sodium phenoxide in the presence of copper; (*d*) by condensation of an *o*-amino-*o*′-methoxybenzophenone,[89] prepared by appropriate steps from anthranilic acid; and (*e*) by subjection of coumarandione[90] to 200° for 6 hr. in an atmosphere of carbon dioxide. Some of these methods are illustrated below. A few others will be mentioned later.



[a] Heat. The intermediate phenoxybenzoic acid is assumed to form. [b] Heated with copper. [c] Heat or H_2SO_4 or $SOCl_2$, $AlCl_3$.



Large R = C_6H_4; small R = $pCH_3C_6H_4SO_2$—.

[a] PCl_5 $mC_6H_4(OCH_3)_2$ + $AlCl_4$. [b] H_2SO_4 + HOAc to remove toluenesulfonyl radical, HNO_2 in H_2SO_4 with heat.

Xanthone melts at 174° and boils at 371°. The compound has some structural resemblance to anthraquinone and resembles[87] the aromatic analogue in some of its chemical properties, modified, however, by the presence of the ethereal oxygen atom in the central ring. For example, nitration takes place much more readily in the xanthone ring. Tri- and tetra-substituted derivatives can be obtained. By contrast, dinitroanthraquinone is not nitrated further. Xanthone is also readily brominated and forms a hexa- and octa-bromo product. Fusion with potassium hydroxide opens the ring to 1,1′-dihydroxybenzophenone; the same process on anthraquinone gives two molecules of benzoic acid. As in γ-pyrone, the carbonyl group is inert to phenylhydrazine or hydroxyl amine. Perchloric acid gives a crystalline perchlorate; sulfuric acid dissolves it with a bright blue fluorescence in a yellow solution. Zinc dust in alcoholic alkali converts it to xanthydrol; zinc-dust distillation or hydriodic acid converts it to xanthene. One molecule of a Grignard reagent adds to xanthone in contrast to two molecules which add to coumarins. Xanthone[91] is toxic to codling moth larvae, even more so than nicotine sulfate in mineral oil.

---

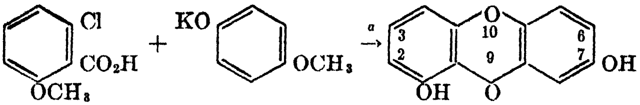
[87] Dhar, *J. Chem. Soc.*, **117**, 1053 (1920); Holleman, *Org.* Syntheses, *Coll. Vol.* I, 552 (1941).

[88] Ullmann and Zlokasoff, *Ber.*, **38**, 2111 (1905); Lock and Kempter, *Monatsh.*, **67**, 24 (1935).

[89] Ullmann and Denzler, *Ber.*, **39**, 4332 (1906).

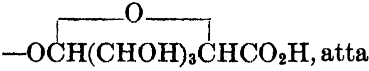
[90] Schonberg, Moubasher and Mostafa, *J. Chem. Soc.*, 348 (1941).

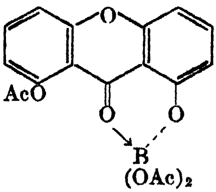
Euxanthone is 1,7-dihydroxyxanthone. It is present as a glucoside in mango leaves. It can be prepared[92] from 2-chloro-6-methoxybenzoic acid by the steps outlined below.



[a] Heat with Cu, H_2SO_4 to form xanthone system, $AlCl_3$ to convert methoxy groups to hydroxy.

When euxanthone is treated with methyl iodide and alkali, only one hydroxyl group is methylated. Distillation of euxanthone with zinc dust gives xanthene.

In one part of India, the urine of cows that have been fed on mango leaves is heated in order to precipitate a pigment known as Indian yellow,[63] which is used for coloring walls and doors and as a water color by artists. The pigment contains 51 per cent of *euxanthic acid*, which has the composition of euxanthone, except for the glucuronic acid,  $-O\overbrace{CH(CHOH)_3CH}^{O}CO_2H$, attached at position 7. Euxanthic acid can be found also in the urine of rabbits and dogs that have been fed euxanthone. The position of the sugar derivative is shown readily by methylation with diazomethane followed by hydrolysis. The sugar is eliminated, and the methyl ether is not the same as that obtained from euxanthone with methyl iodide and alkali.[93] The 1-hydroxy group is also distinguished by its capacity to form a boroacetate with boroacetic acetic anhydride. A chelated structure is formed. The 6-hydroxy group is acetylated during this process. The complex is subsequently decomposed by warm water with the formation of 6-acetyleuxanthone. Methylation



with diazomethane and subsequent hydrolysis then gives 4-methyleuxanthone, isomeric with the product of methylation of euxanthone with methyl iodide and alkali.

---

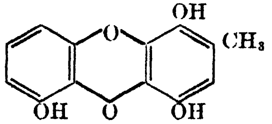
[91] Smith, *Ind. Eng. Chem.*, **34**, 499 (1942).

[92] Ullmann and Panchaud, *Ann.*, **350**, 108 (1906).

[93] Robertson and Waters, *J. Chem. Soc.*, 1709 (1931).

Gentisen is the 3-methyl ether of 1,3,7-trihydroxyxanthone. It is present as a glucoside in the rhizomes of *Gentiana lutea* L.

Ravenelin is a yellow crystalline pigment, $C_{14}H_{10}O_5$, formed from a species of *Helminthosporium* grown on glucose. One of the subgenus of this mold produce polyhydroxyanthraquinones and another produces polyhydroxyxanthones.[94] This last subgenus includes *H. ravenelii,* a parasite that grows on grass, and *H. turicicum,* the leaf blight that grows on maize. Ravenelin is 3-methyl-1,4,8-trihydroxyxanthone. It melts at 267 to 268°, forms a ferrichloride salt $C_{17}H_{17}O_5{\cdot}FeCl_4$, and forms a triacetyl or benzoyl derivative. The trimethyl ether is inert to alkali and acetic anhydride. Fusion with potassium hydroxide gives resorcinol. Treatment of the trimethyl ether in boiling xylene with sodamide gives urea and 2,5,3′-trimethoxy-3-methyldiphenyl ether. Excess bromine converts the ether to a tri- and a tetra-bromo product. The latter is compared with a synthetic product.

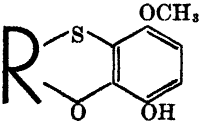


Thioxanthone.—The thioxanthones are the sulfur analogues of the xanthones. They are prepared[95] by analogous methods, as illustrated by the equations below.

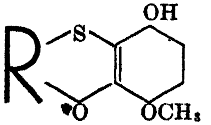
$$p\text{-}NO_2C_6H_4Cl + Na_2S \rightarrow NaCl + p\text{-}NO_2C_6H_4SNa$$
$$p\text{-}NO_2C_6H_4SNa + o\text{-}ClN^2C_6H_4COOH \rightarrow NaCl + N_2 + p\text{-}NO_2C_6H_4SC_6H_4COOH$$
$$p\text{-}NO_2C_6H_4SC_6H_4COOH + PCl_5 \rightarrow p\text{-}NO_2C_6H_4SC_6H_4COCl + HCl + POCl_3$$
$$p\text{-}NO_2C_6H_4SC_6H_4COCl + \text{heat} \rightarrow 8\text{—}NO_2C_6H_3\left\{\begin{matrix}S\\C(O)\end{matrix}\right\}C_6H_4 + HCl$$

The basic character[96] of the thioxanthone nucleus becomes greater as methoxy groups are introduced. The positions of hydroxy and methoxy groups are important. A marked contrast in behavior is found in the compounds below.

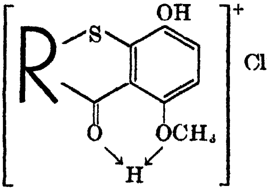
A



B



C



1-Hydroxy-4-methoxythioxanthone (*A*) is insoluble in aqueous alkali and adds no hydrochloric acid. The isomeric 1-methoxy-4-hydroxy compound dissolves in aqueous hydrochloric acid and sodium hydroxide and adds two molecules of hydrochloric acid to form crimson colored salts. The third formula (*C*) shows the chelated structure of the hydrochloric acid addition compound. Similar chelated structures are possible with stannic chloride and boroacetate.

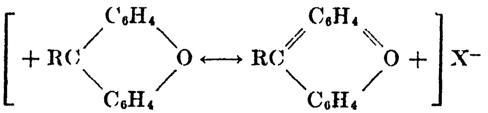
---

[94] RAISTRICK, ROBINSON, and WHITE, *Biochem. J.*, **30,** 1303 (1936).

[95] MAYER, *Ber.*, **42,** 3046 (1909).

[96] ROBERTS and SMILES, *J. Chem. Soc.*, 1322 (1929).

Xanthydrols.—Reduction of xanthone with zinc dust and alkali or by sodium amalgam gives a xanthydrol. The reaction of xanthones with the Grignard reagent gives the homologues of xanthydrol. These compounds dissolve readily in mineral acids and form salts with hydrochloric acid, ferric chloride, platinic chloride, mercuric chloride, etc. The cation is probably a resonance form of oxonium and carbonium structures.



When an aqueous hydrochloric acid solution is treated with vanadous chloride,[97] the dixanthyl is precipitated.

$$2[O(C_6H_4)_2CR]^+Cl + 2VaCl_2 \rightarrow O(C_6H_4)_2CR—CR(C_6H_4)_2O + 2VaCl_3$$

Chromous chloride acts similarly. The dixanthyl will dissociate into free radicals, the more so if R is a branched alkyl group or is an aromatic group.

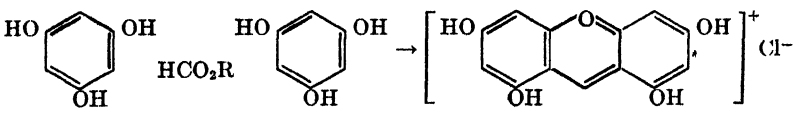
Xanthydrol melts at about 122 to 124°. When heated in ligroin for a long time, it forms the dixanthyl ether, $O(C_6H_4)_2CH—O—CH(C_6H_4)_2O$. The hydroxyl group is very active and is eliminated by condensations with compounds that have active hydrogen atoms such as malonic esters, sulfonamides, and hydrochloric acid, to yield 1:1 products, or with urea and hydrogen sulfide, to yield 2:1 products such as $C_{13}H_9O—S—C_{13}H_9O$. The N-xanthyl-*n*-alkylsulfonamides,[98] derived from the reaction of xanthydrol with alkyl-substituted benzenesulfonamides, have melting points that are suitable for characterization of the latter.

Xanthylium Salts.—A large number of xanthylium salts are obtained by condensation of polyhydroxybenzene compounds with ethyl formate, the orthoformate, or a like compound under the influence of hydrochloric acid. One resonance form of the yellow colored product is represented below.

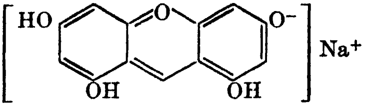
---

[97] Conant and Sloan, *J. Am. Chem. Soc.*, **45**, 2466 (1923); **47**, 572 (1925); Conant, Small, and Sloan, *ibid.*, **48**, 1743 (1926); Ziegler, Fries, and Salzer, *Ann.*, **448**, 248 (1926).

[98] Phillips and Frank, *J. Org. Chem.*, **9**, 9 (1944).

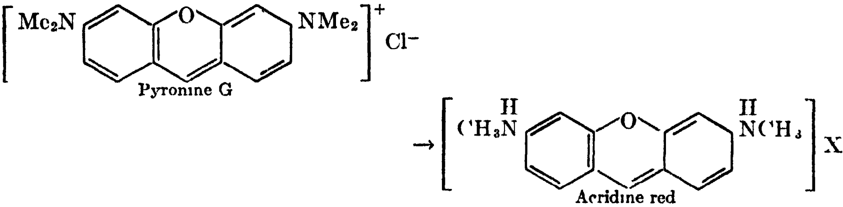


When the xanthylium salt is treated with alcoholic potassium acetate, the color changes to an orange red. One possible resonance form is shown below.

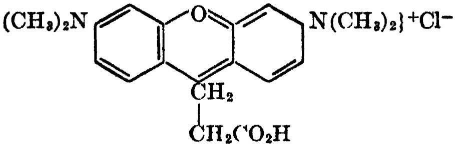


If formaldehyde had been used in the above condensation instead of ethyl formate, the product would have been a xanthene, which, with chloranil in acetic acid and then with hydrochloric acid, is converted to the xanthylium chloride.

Pyronine.—If *m*-dimethylamino phenol is allowed to condense with formaldehyde, a xanthene is produced, which on oxidation and conversion to the hydrochloride gives pyronine. One resonance form is shown below. Permanganate oxidation converts this compound to a red compound called acridine red.[99]


Pyronine G
Acridine red

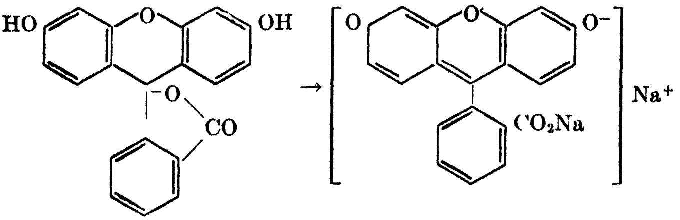
If succinic anhydride with zinc chloride is used in place of formaldehyde, the product is the succinyl derivative which is more important as a dyestuff.


Rhodamine S

Eosines.—*Fluorescein* was first prepared in 1871 by fusion of a mixture of phthalic anhydride and resorcinol. It has a yellow color when precipitated from alkaline solution with acid and a red color when crystallized from alcohol. Fluorescein has a lactoid formula. When treated with alkali, it has a quinoid formula. It owes its fluorescence in alkaline solution to resonance between two forms, one of which is shown below.

---

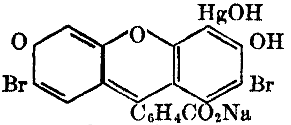
[99] Cain and Thorpe, "The Synthetic Dyestuffs," Griffin & Company, Ltd., London, 1933.



The behavior is analogous to that of phenolphthalein. Fluorescein is used as a diagnostic agent in ophthalmological work to delineate corneal ulceration.[100]

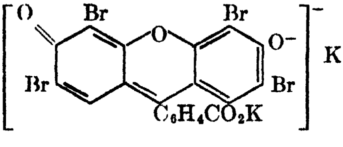
Orcinolphthalein[101] is obtained from orcinol and phthalic anhydride by fusion at 210 to 220° or by treatment with concentrated sulfuric acid at 135°.

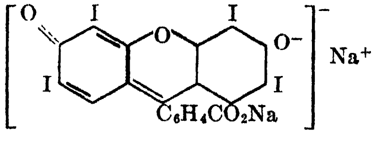
Mercurochrome is a mercurated dibromofluorescein which is used as a diuretic and an antiseptic. It is inferior to iodine as a skin disinfectant.



Mercurochrome

Eosin and *erythrosin* are the alkaline salts of a tetrabrominated and tetraiodinated fluorescein, respectively.





The latter is a red dye, the use of which is permitted in food. It is also used as a photographic sensitizer.[102]

Rhodamines.—Rhodamine dyes[99] are the phthalein analogue of pyronine. They are prepared by the condensation of phthalic anhydride with a dialkyl-*m*-aminophenol.

---

[100] GOODMAN and GILMAN, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

[101] ORNDORFF and ALLEN, *J. Am. Chem. Soc.*, **37**, 1201 (1915); ORNDORFF and HEMMER, *ibid.*, **49**, 1272 (1927).

[102] MEES, "The Theory of the Photographic Process," The Macmillan Company, 1942.

Problems

1. What is the product produced from the following reactions? (*a*) 2-Chloro-5-methoxybenzoic acid with the alkali salt of β-naphthol and copper at 180 to 200° followed by treatment with sulfuric acid.[88] (*b*) Anthranilic acid treated successively with benzenesulfonyl chloride, phosphorus pentachloride, veratrole, sulfuric acid, nitrous acid, and heat.[89] (*c*) Phloroglucinol and salicylnitrile subjected to a Hoesch synthesis and the product hydrolyzed with hot aqueous sodium hydroxide.[103] (*d*) Pyrogallol and diacetyl-β-resorcylonitrile treated with zinc chloride and hydrochloric acid followed by boiling 2 *N* sodium hydroxide.[104]

2. What is the product formed in the following reactions? (*a*) Equivalent quantities of salicyl aldehyde, sodium succinate, and acetic anhydride, heated together, give $C_{18}H_{10}O_4$.[105] (*b*) 2-Methyl-1,4-naphthohydroquinone (how prepared?), when treated in sequence with (1) methyl sulfate in alcoholic potassium hydroxide solution, (2) concentrated hydrochloric acid and formaldehyde in a stream of hydrogen chloride at 70°, (3) ethyl sodioacetoacetate in ethanol followed by acidification, (4) aqueous 7 per cent sodium hydroxide followed by reflux in methanol and acidification again, (5) methylmagnesium iodide followed by hydrobromic-acetic acid reflux gives[106] $C_{16}H_{18}O_2$. (*c*) ω-Hydroxy acetophenone (how obtained?) when treated in sequence with (1) O-tetraacetyl-α-glucosidyl bromide and anhydrous silver carbonate in boiling ether, (2) β-resorcyl aldehyde at room temperature for 96 hr. in dry ether saturated with hydrogen chloride, (3) methyl alcoholic-ammonia at 0° for 14–15 hr., (4) methyl alcoholic hydrochloric acid.[107] (*d*) Salicylaldehyde, treated in sequence with ethyl acetoacetate, nitrous acid, and phosphorus trichloride gives $C_{11}H_9NO_3$.[108] (*e*) 2,4-Dihydroxyphenylbenzyl ketone, heated with cinnamic anhydride and sodium cinnamate at 170 and up to 250° for 5 hr. gives $C_{32}H_{22}O_4$, which by hot alcoholic potassium hydroxide, followed by methyl sulfate, potassium permanganate, acid, and heat gives $C_{16}H_{12}O_3$.[109] (*f*) Duroquinone (tetramethyl-*p*-benzoquinone), treated with diethyl malonate and sodium in benzene, gives, after acidification, a yellow compound that has the composition $C_{15}H_{18}O_5$.[110]

3. *n*-Hexylaldehyde is treated with acetone and sodium hydroxide, followed by successive treatments with ethyl malonate, sodium ethoxide, aqueous potash, mineral acid, and heat. The $C_{11}H_{18}O_2$ product of this sequence of reactions is sometimes called "dihydro olivetol." It condenses with 2-bromo-4-methylbenzoic acid (how prepared?) in the presence of copper to form a compound, which by successive treatments with sulfur at 255 to 260° and then with methylmagnesium iodide yields $C_{21}H_{26}O_2$. What are the compounds formed in these reactions?[85]

4. Trimethyl hydroquinone, when heated with γ,γ-dimethylallyl bromide (how obtained?), gives $C_{14}H_{20}O_2$. Show how the same product can be prepared by way of an intermediate coumarin. Show also how it might be obtained by condensation of an appropriate compound with isoprene.[111]

[103] Nishikawa and Robinson, *J. Chem. Soc.*, **121,** 839 (1922).

[104] Atkinson and Heilbron, *ibid.*, 2688 (1926).

[105] Dyson, *J. Chem. Soc.*, **51,** 61 (1887).

[106] Smith, Wawzonek, and Miller, *J. Org. Chem.*, **6,** 229 (1941).

[107] Robertson and Robinson, *J. Chem. Soc.*, 242 (1927).

[108] Linch, *ibid.*, **101,** 1758 (1912).

[109] Baker and Robinson, *ibid.*, **127,** 1981 (1925).

[110] Smith and Dobrovolny, *J. Am. Chem. Soc.*, **48,** 1693 (1926); Smith and Denyes, *ibid.*, **58,** 304 (1936).

[111] Smith, Ungnade, Hoehn, and Wawzonek, *J. Org. Chem.*, **4,** 305, 311 (1939).

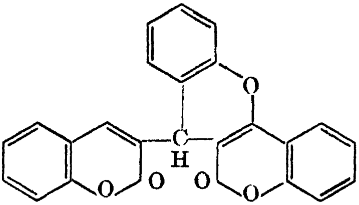
5. 4,6-Dibromo-o-cresol is treated with chromic acid in acetic acid at 60° to form a product, which by successive treatments with (*a*) stannous chloride and (*b*) alkali and methyl sulfate gives a product *A*, $C_9H_{11}O_2Br$. In another sequence of reactions, 2-hydroxy-4-methoxybenzaldehyde is treated with hydroxylamine and then in sequence with (*a*) boiling acetic anhydride, (*b*) hot 10 per cent sodium hydroxide, (*c*) hydrochloric acid to form a product *B*, $C_8H_7NO_2$. *A* and *B* are then treated with potassium and copper bronze and the mixture heated to 200° for 8 hr., followed by treatments with (*a*) aqueous barium hydroxide, (*b*) phosphorus oxychloride, (*c*) heat. The final product[94] has the composition $C_{17}H_{16}O_5$.

6. 2-Hydroxy-1-acetonaphthone, $HO—C_{10}H_6—C(O)CH_3$, anisoyl chloride, and pyridine are heated together for 1 hr. and then poured into hydrochloric acid. The product is then treated at room temperature for 15 min. in an alcohol solution that contains sodium ethoxide, after which the mixture is poured into acetic acid. The $C_{20}H_{16}O_4$ product of this last reaction is allowed to stand in glacial acetic acid with hydrogen bromide to form $C_{20}H_{14}O_3$. What products are formed?[112]

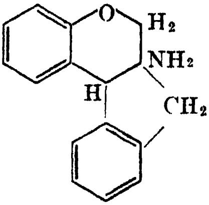
7. Devise a method for the synthesis of 2-methyliriginol, which is 2-methyl-5,6,7,-3′,4,5′-hexahydroxyisoflavone.[113] Use guaiacol and gallic acid as starting materials.

8. Suggest a method for the preparation of selenoxanthone and phenylselenoxanthydrol.[114]

9. Suggest a method for the preparation of the compound[115] shown below. Name the compound.



10. μ-Aminochromidan has the same carbon framework found in hematoxylin.



The heterocyclic ring is prepared by condensation of an appropriate phenoxy acid.[116] Suggest an acid that would be suitable and outline steps that would be necessary to complete the synthesis.

---

[112] Ullal, Shah, and Wheeler, *J. Chem. Soc.*, 1499 (1940).

[113] Baker and Robinson, *ibid.*, 152 (1929).

[114] Francois, *Compt. rend.*, **190,** 191 (1930).

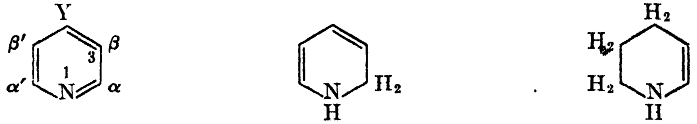
[115] Sullivan, Huebner, Stahmann, and Link, *J. Am. Chem. Soc.*, **65,** 2288 (1943).

[116] Pfeiffer and Epler, *Ann.*, **546,** 263 (1941).

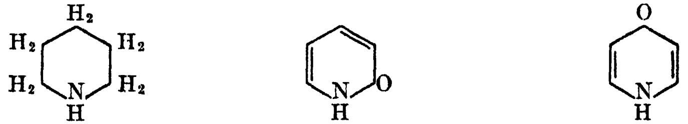
CHAPTER VIII

THE PYRIDINE GROUP

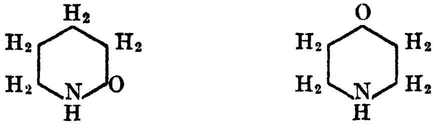
The pyridine series of bases was first discovered by Anderson[1] in 1846 while he was attempting to confirm Runge's observation of pyrrol in the sulfuric acid wash of the naphtha obtained from coal tar. These washings, neutralized with ammonia and distilled, did indeed give a positive pine-splinter test; but, in addition, the distillate contained a new compound, which, after further distillations and digestion with potash, boiled at 272°F and yielded a pure solid derivative with platinic chloride. Analysis showed that the base had the composition C_6H_7N (then expressed as $C_{12}H_7N$) and was, therefore, isomeric with aniline. The new product was called "picoline." Bone oil proved a more fruitful source, for he obtained more from 300 lb. of bone oil than from several hundred gallons of coal-tar naphtha. After much labor, he separated[2] not only picoline, C_6H_7N, but also pyridine, C_5H_5N, lutidine, C_7H_9N, and collidine, $C_8H_{11}N$, in addition to methyl, ethyl, propyl, and butylamine. All these aromatic bases were characterized by formation and analysis of the sulfate, hydrochloride, and nitrate salts and by conversion to the double salts of platinic chloride. The work is an excellent example of the separation of pure compounds from crude material in that comparatively early period.



Pyridine 1,2-Dihydropyridine Δ₂-Tetrahydropyridine



Piperidine or hexahydropyridine α or 2-Pyridone γ- or 4-Pyridone



α-Piperidone γ-Piperidone

FIG. 1.—Naming and numbering of pyridine compounds.

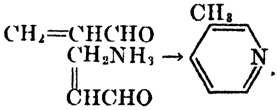
---

[1] ANDERSON, *Trans. Roy. Soc. Edinburgh*, **16**, 123 (1849).

[2] ANDERSON, *ibid.*, **20**, 247 (1853); **21**, 219 (1857).

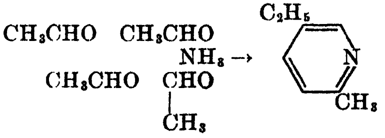
The cyclic structure of pyridine was not recognized until 1870 when Körner[3] concluded that it contained a piece of the benzene system and was best represented as a ring compound.

Methods of Synthesis. *Ring Closure with Ammonia.*—One of the earliest methods of synthesis was developed by Baeyer,[4] who reasoned that the comparatively large amount present in bone oil must be caused by a reaction of acrolein, from pyrolysis of the glycerin in fats, with ammonia from nitrogenous material. He, accordingly, passed acrolein vapors into ammonia, evaporated the solution to dryness, and heated the residue in quantities of 200 to 300 g. in a copper retort. The products were a voluminous coke and an aqueous distillate from which an oil was recovered which boiled around 132° and formed crystals of a platinate salt, $(C_6H_8NCl_3)_2Pt$, identical with the picoline isolated from bone oil. Formation occurs according to the general scheme shown below.



By a similar reaction, crotonaldehyde ammonia yields one of the collidines.

The preparation is not limited to unsaturated aldehydes. Aldehyde ammonia combines according to the following plan to form 2-methyl-5-ethylpyridine. Obviously a great excess of ammonia is unnecessary. Better yields are in fact obtained from aldehyde ammonia and paraldehyde.[5] Propionaldehyde, ammonia, and paraldehyde yield parvolin,



a dimethylethylpyridine. Some piperidines are formed also in the reaction. The same principle underlies the formation of β-picoline, contaminated with some of the α-isomer, by pyrolysis of a mixture of glycerine, ammonium phosphate, and phosphorus pentoxide.[6] The yield, however, is only 20 g. from 250 g. of glycerol.

Similar condensations[7] with saturated aldehydes occur catalytically over alumina and related oxides. Ammonia with acetaldehyde forms α- and β-picoline; with propionaldehyde the 2-ethyl and 4-ethyl-3,5-dimethylpyridine. Pyridine is formed from one part of formaldehyde, two of acetaldehyde, and one of ammonia. Two molecules of acetone with one of ammonia yields 2,4,6-trimethylpyridine. A mixture of benzaldehyde, acetaldehyde, and ammonia at 305 to 310° over alumina or kaolin similarly yield α- and γ-phenylpyridine.[8] The reaction is general, and the pyridine ring usually forms from the α- or the α- and β-carbon atoms of the aldehydes.

---

[3] Körner, cited by Baeyer, *Ann.*, **155**, 282 (1870).

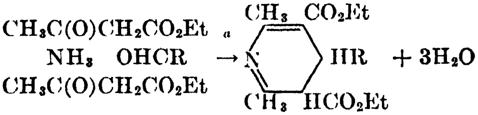
[4] Baeyer, *Ber.*, **2**, 398 (1869); *Ann.*, **155**, 281, 294 (1870).

[5] (*a*) Dürkoff, *Ber.*, **20**, 444 (1887); (*b*) Dürkoff and Schlaugh, *ibid.*, **21**, 832 (1888); (*c*) Dürkoff and Göttsch, *ibid.*, **23**, 685 (1890).

[6] Schwartz, *ibid.*, **24**, 1676 (1891).

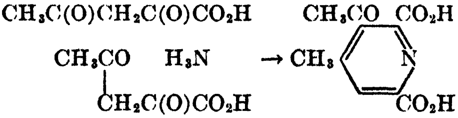
[7] (*a*) Chichibabin, *J. Russ. Phys. Chem. Soc.*, **37**, 1229 (1905); *Chem. Cent.*, **1**, 1438, (1906); (*b*) Chichibabin, *J. Russ. Phys. Chem. Soc.*, **47**, 703 (1914); *Ber.*, **60**, 1873 (1927); (*c*) *Bull. soc. chim.* [5], **3**, 762 (1936).

The above methods might be considered as the action of ammonia on unsaturated aldehydes or on systems capable of forming these reagents. Such processes contrast with those in which ammonia reacts with molecules that have two carbonyl groups or a carbonyl and carboxyl group or other equivalent. For example, the method of Hantzsch[9] is very specific. A 1,3-keto ester, such as ethyl acetoacetate is condensed with ammonia and aldehyde according to the scheme



[a] This reaction, and many of the subsequent ones, can be regarded as proceeding by condensation of the active carbonyl group of one molecule with the active methylene group of another molecule to give a 1,5-diketone as the initial product. This intermediate then reacts with ammonia to give a ring in the same way that the 1,4-diketones give pyrroles. This type of condensation provides a contrast with that shown in the two previous illustrations in which the condensation begins with the reaction of ammonia with the aldehyde group. The position of the pyridine ring is turned end for end in these cases, partly to simplify the problem of remembering the two types and the position of the substituents, but more to conform with the conventional order of writing the formulas of the aliphatic reagents.

The dihydropyridine product can be oxidized readily to the pyridine derivative by nitric acid. Aldehydes, keto esters, β-diketones, or other like compounds may be used in this synthesis. The condensation of acetylpyruvic[10] acid with ammonia is similar except that no



aldehyde is needed and the product is a pyridine compound, not a dihydro one.

Knoevenagel's[11] reaction looks a little like Hantzsch's carried out

---

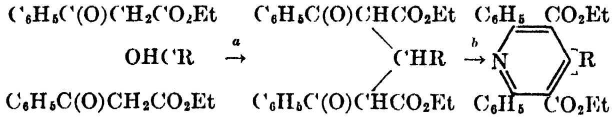
[8] CHICHIBABIN and OROCHKO, *J. Russ. Phys. Chem. Soc.*, **62**, 1201 (1930); *C.A.*, **25**, 2725 (1931).

[9] HANTZSCH, *Ann.*, **215**, 1 (1882); *Ber.*, **18**, 1744 (1885); ENGLEMANN, *Ann.*, **231**, 50 (1885); CLAISEN, *ibid.*, **297**, 39 (1897).

[10] MUMM and BERGELL, *Ber.*, **45**, 3040 (1912).

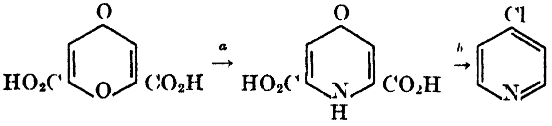
[11] KNOEVENAGEL, *Ann.*, **281**, 25 (1894).

stepwise. The carbon segments of the ring are first joined under the influence of piperidine or diethyl amine, and the nitrogen atom is then put in place by heating the dioxime rather than by condensing with ammonia. Ethyl benzoylacetate or desoxybenzoin may thus be condensed with aldehydes to give a wide variety of 1,5 diketones which can be converted to the pyridine derivative, but a methyl group in the sixth position to a carbonyl causes a keto cyclohexene to form.

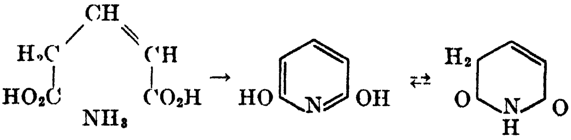


[a] R_2NH. [b] H_2NOH, heat

Any 1,5-dicarbonyl system, which will or has formed a pyrone, changes to a pyridine compound when heated with ammonium hydroxide. In other words, methods for synthesis of pyrones become useful also for the preparation of pyridones, as illustrated by the change of chelidonic to chelidamic acid.[12] Similarly, an anhydride (glutaconic acid), heated with ammonia, yields 2,6-dihydroxypyridine[13] which is in equilibrium with the isomeric cyclic imide. The true pyridine character of this compound is confirmed by (*a*) the dibenzoyl derivative obtained by a Schotten-Baumann reaction, (*b*) the deep reddish violet color observed with ferric chloride characteristic of phenols, (*c*) the blue fluorescent phthalein produced when fused with phthalic anhydride, a change typical of the behavior of a resorcinol, and (*d*) the azo dyestuffs formed with diazonium salts. The tautomeric imide state is indicated by formation of an isonitroso derivative (a monoxime).



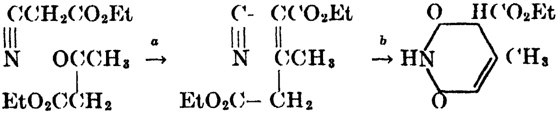
[a] NH_4OH. [b] Decarboxylation, $POCl_3$.



Ring Closure with Compounds that Contain Nitrogen.—Nitriles, amides, and amines, which have appropriately placed carbonyl groups and hydrogen atoms, can be used for synthesis of pyridine compounds. When only one nitrogen atom is present in the molecule, the mode of combination is easy to predict. For example, ethyl cyanoacetate condenses with ethyl acetoacetate: first under the influence of sodium to link the two carbons together (the very active methylene of the former at the active carbonyl of the latter), and then under the influence of aqueous acid to join the ring[14] at the nitrogen atom, presumably by way of hydrolysis of

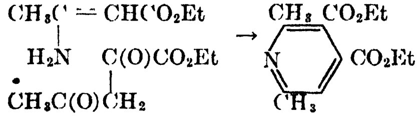
---

[12] ROBINSON and THORNBY, *J. Chem. Soc.*, 2169 (1924).
[13] THORPE, *ibid.*, 87, 1669 (1905).



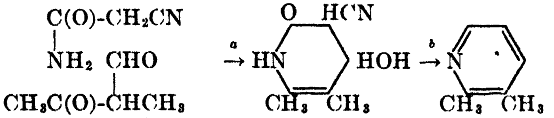
ᵃ Na. ᵇ HX + H_2O.

the nitrile to the amide. Other keto esters and diketones can be used in place of ethyl acetoacetate with consequent increase in the variety of products. Similarly, ethyl β-aminocrotonate, made by saturating an ethereal solution of ethyl acetoacetate with ammonia,[15] condenses so readily with diketo esters that the two need only to be shaken together in the cold to prepare a pyridine compound after the following manner.



Since alkoyl pyruvic esters are readily prepared from ethyl pyruvate and acid chlorides, the method is valuable for the preparation of 2-methyl-6-alkyl (or aryl) pyridines.[16]

If two nitrogen atoms, such as in a cyano and amide or a cyano and amino group, are present together in the same molecule, the nitrile is less apt to provide the ring nitrogen than are the other two functions. For example, cyanoacetamide and 3-formyl-2-butanone (itself obtained by help of sodium from methyl ethyl ketone and ethyl formate) yield a cyanopyridone,[17] convertible in subsequent stages to 2,3-dimethylpyridine. Diketo and keto ester compounds can be used in this reaction.



ᵃ Piperidine. ᵇ Hot conc. HCl causes hydrolysis of the nitrile group and simultaneous dehydration: decarboxylation by heat at 325–335°. $POCl_3$, Pd + H.

---

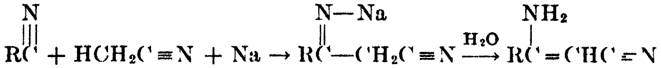
[14] Rogerson and Thorpe, *ibid.*, **87,** 1685 (1905).

[15] Collie, *Ann.*, **226,** 301 (1884).

[16] Mumm and Hüneke, *Ber.*, **50,** 1568 (1917); Mumm and Böhme, *Ibid.*, **54,** 726 (1921).

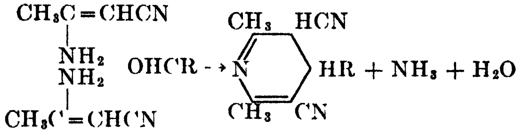
[17] Tracy and Elderfield, *J. Org. Chem.*, **6,** 63 (1941).

So also does the amino group take precedent over the nitrile in the use of the dinitrile. These reagents are really amino nitriles but are called "dinitriles" because they are condensation products of acetonitrile with itself or another nitrile under the influence of sodium. Two molecules

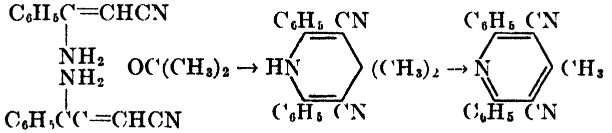


$$R\overset{N}{\overset{|||}{C}} + HCH_2C\equiv N + Na \rightarrow R\overset{N-Na}{\overset{\|}{C}}-CH_2C\equiv N \xrightarrow{H_2O} R\overset{NH_2}{\overset{|}{C}}=CHC\equiv N$$

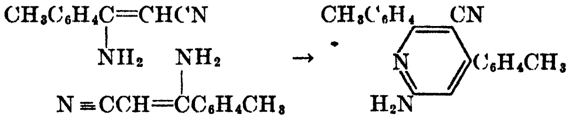
a dinitrile, illustrated below by the simplest one, may condense[18] with an aldehyde in a manner essentially identical with Hantzsch's method.



If the aldehyde is replaced by a ketone such as acetone, the product is a dihydropyridine compound[19] that can subsequently be oxidized by chromic acid in acetic acid solution to a pyridine derivative.



In the absence of an aldehyde or ketone, a dinitrile can condense[20] with itself in hot acetic acid. An amino nitrogen is again favored to become the hetero ring atom. Unlike ends join.



Preparation from Piperidines.— Piperidine and partially reduced pyridines can be converted readily to pyridine compounds by dehydrogenation with (*a*) zinc dust,[21] preferably with the pyridine salt; (*b*) palladium on asbestos[22] at 270 to 280°; (*c*) platinum on asbestos[23] at 320 to 330°; or (*d*) catalytic nickel at 250°.[24] Oxidizing agents such as bromine,[25] nitrobenzene[26] at 250 to 260°, concentrated sulfuric acid[27] at 300°, and silver acetate[28] in 10 per cent acetic acid at 180° have also been successfully employed.

---

[18] v. Meyer, *J. prakt. Chem.* [2], **78**, 497 (1908).

[19] v. Meyer, *ibid.* [2], **92**, 174 (1915).

[20] Meyer, Berger, Oehler, and Schletter, *ibid.*, **90**, 29 (1914).

[21] Hofmann, *Ber.*, **17**, 825 (1884); Ahrens, *ibid.*, **26**, 3035 (1893).

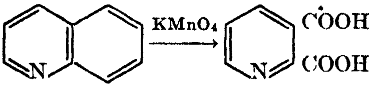
[22] Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

[23] Ehrenstein, *Ber.*, **64**, 1137 (1931).

[24] Sabatier and Mailhe, *Compt. rend.*, **144**, 786 (1907).

[25] Hofmann, *Ber.*, **16**, 588 (1883).

From Condensed Ring Systems.—Another method, used often to locate substituents on a quinoline, isoquinoline, or other condensed system, is to oxidize with potassium permanganate. The greater stability of the pyridine nucleus protects that portion of the compound while the aromatic ring is broken.



Many di- and poly-carboxylic acids are obtained by this manner.

Miscellaneous Syntheses.—Pyridine compounds can be prepared also by a number of miscellaneous but interesting methods. Among these are (*a*) the condensation of acetylene with hydrocyanic acid[29] in a hot tube; (*b*) the passage of N-methyl or 2-methylpyrrole through a hot tube;[30] (*c*) the conversion of amyl nitrate to pyridine[31] under the dehydrating action of phosphoric acid; (*d*) the ring enlargement to β-chloropyridine[32]

$$C_5H_{11}NO_3 \xrightarrow{H_3PO_4} C_5H_5N + 3H_2O$$

which occurs when pyrroles are treated with chloroform and alkali; (*e*) the dehydration of a mixture of acetamide and glycerol[33] over phosphorus pentoxide; (*f*) the reaction of glucose with ammonium sulfate, chloride, or oxalate at 155 to 165° to give 2-methyl-5-hydroxypyridine,[34] a change that probably occurs by way of 5-hydroxymethyfurfural.

Chemical Reactions.—The reactions of pyridine can be considered as centered largely in the special properties conferred by the presence of nitrogen. This atom exerts its influence (*a*) as a positive pole in acid solutions to suppress substitution in the nucleus; (*b*) in an ammono aldehyde, (C═N), system[35] by which some characteristic addition reactions are favored; and (*c*) as a reactive ammonium salt from which numerous transformations are possible, some of which lead to ring opening. These properties are blended with those of an aromatic ring which cause the compound to exhibit the stability characteristics of a conjugated cyclic system.

---

[26] Lellmann and Geller, *ibid.*, **21**, 1921 (1888).

[27] Koenigs, *ibid.*, **12**, 2341 (1879).

[28] Tafel, *ibid.*, **25**, 1619 (1892).

[29] Ramsey, *Phil. Mag.* [5], **2**, 269 (1876); **4**, 24 (1877); Meyer and Tanzen, *Ber.*, **46**, 3183 (1913).

[30] Pictet, *ibid.*, **38**, 1946 (1905).

[31] Chapman and Smith, *Ann. Suppl. Bd.*, **6**, 329 (1868).

[32] Ciamician and Dennstedt, *Ber.*, **14**, 1154 (1881); *Gazz. chim. ital.*, **11**, 300 (1881).

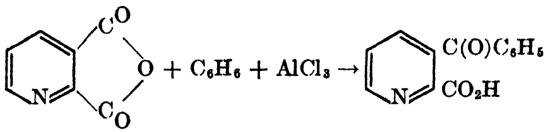
[33] Zanoni, *Ber.*, **15**, 528 (1883); Hesekial, *ibid.*, **18**, 910, 3091 (1885).

[34] Aso, *J. Agr. Chem. Soc. Japan*, **16**, 249, 253 (1940); *C.A.*, **34**, 6278, 6940 (1940).

[35] Decker and Kaufman, (*a*) *J. prakt. Chem.*, **84**, 219 (1911); (*b*) Franklin, *J. Am. Chem. Soc.*, **46**, 2150 (1924); Strain, *ibid.*, **49**, 1558 (1927); **54**, 1221 (1932).

The Positive Pole and Substitution Reactions.—The effect of a positive pole[36] attached to an aromatic system is twofold: it retards the rate of substitution and directs an entering group to a meta position. The nearer the pole to the ring, the more pronounced these effects. It is not surprising, therefore, that a positive pole on a corner of the ring makes substitution in pyridine extremely difficult. The fuming nitric and sulfuric acid mixture that successfully nitrates trimethylanilinium salts is without effect on pyridinium salts. Not until a solution of potassium nitrate in nitric acid is dropped into a solution of pyridine in 100 per cent sulfuric acid at 300° in the presence of iron as a catalyst can nitration[37] occur. Even then the yield is no better than 22 per cent. The directive influence is, of course, meta, *i.e.*, to C_3. So also does sulfonation[38] need 40 hr. heating with 100 per cent sulfuric acid at 300° or a day-long period at 320 to 330° in order to obtain the 3-sulfonic acid.

Since the common substitution reactions such as nitration, sulfonation, and halogenation occur in acid media, it is not surprising that the methods which are successful with an aromatic nucleus fail in the case of an unsubstituted pyridine. Even such a vigorous reagent as the Friedel-Crafts fails to attach a benzoyl group to pyridine, although there is no resistance to use of a pyridyl compound, as pictured below, with benzene, toluene, naphthalene, or other aromatic nucleus.[39] The reaction of mercuric chloride is likewise difficult. It requires a temperature of 170° and produces a β-mercuric chloride derivative, though this reagent causes some orthomercuration in nitrobenzene.[40] Even in the gaseous phase at 115 to 120°, a mixture of pyridine,[41] nitric acid, and carbon dioxide passed together through a tube with or without ultraviolet illumination



---

[36] INGOLD, *Ann. Repts.*, **23**, 129 (1926).

[37] FRIEDL, *Ber.*, **45**, 428 (1912); *Monatsh.*, **34**, 759 (1913); KIRPAL and REITER, *Ber.*, **58**, 699 (1925).

[38] FISCHER, *ibid.*, **15**, 62 (1882).

[39] JEPHCOTT, *J. Am. Chem. Soc.*, **50**, 1189 (1928).

[40] KOBE and DOUMANI, *Ind. Eng. Chem.*, **33**, 170 (1941).

[41] SCHORIGIN and TOPTSCHIEW, *Ber.*, **69**, 1874 (1936).

yields 7 to 10 per cent only of a 3-nitro product. At 300 to 330°, the mixture explodes.

Pyridine can, however, be brominated[42] or chlorinated directly by a vapor-phase process over charcoal or pumice at 300°. The product is a mixture of 3-bromo- or 3,5-dibromo-pyridine in a combined yield of 50 per cent. At this relatively low temperature, catalysts have an effect on the position of the entering group. Ferrous bromide produces the 3- and 3,5-products, cuprous bromide the 2-and 2,6-compounds. At 500°, these metal salts are valueless, either because they are volatilized, or become coated with carbonaceous product. Chlorination proceeds in a similar way.

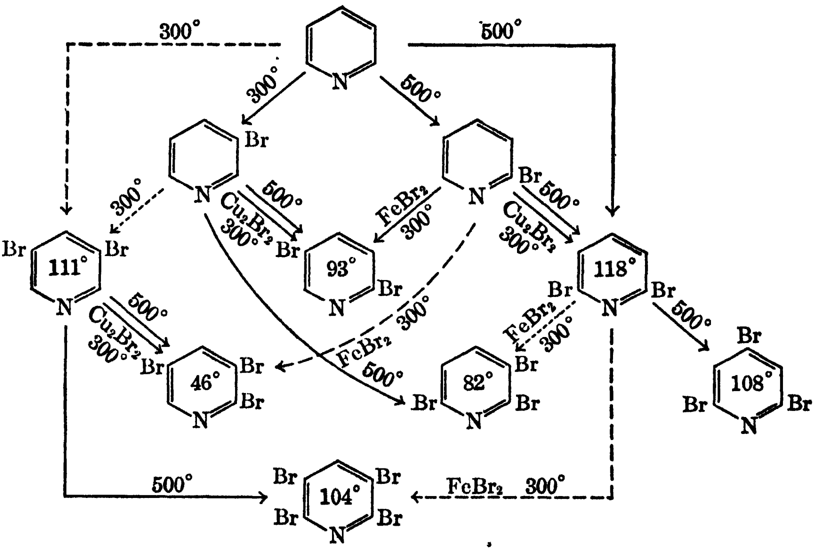


FIG. 2.—Products of vapor-phase bromination of pyridine. Dotted lines indicate substitution at 3- or 5-positions; solid lines indicate substitution at 2-, 4-, or 6-positions.

If substitution could be carried out in an alkaline rather than an acid medium, the retarding effects of a positive pole might be avoided, or reduced, and the customary reaction of a conjugated six-membered ring would be expected. It is not surprising, therefore, that aryl groups can be introduced readily into pyridine by means of the diazonium reaction.[43] The process is best carried out by slow addition of a solution of phenydiazonium salt to an aqueous alkaline solution of pyridine at

$$RN_2OH + C_5H_5N \rightarrow \alpha,\beta, \text{ or } \gamma\text{—}RC_5H_4N + N_2 + H_2O$$

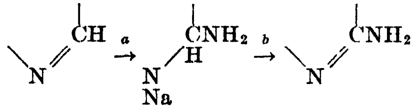
---

[42] DEN HERTOG and WIBANT, *Rec. trav. chim.*, **51**, 382, 940 (1932); WIBAUT and BICKEL, *ibid.*, **58**, 994 (1939).

[43] HAWORTH, HEILBRON, and HEY, *J. Chem. Soc.*, 349, 358 (1940); BUTTERWORTH, HEILBRON, and HEY, *ibid.*, 555 (1940).

temperatures that vary from 20 to 70°, depending on the amine used. This type of reaction is successful with a very large number of substituted benzene diazonium salts, and yields vary from 20 to 80 per cent. Substitution occurs in all positions, but predominantly in the alpha. The somewhat random position taken by the entering group suggests that the agent may be a free radical or merely that the strong meta-directing influence has been largely removed. No reaction occurs when a methohalide or sulfate of pyridine is used; and this fact emphasizes again the repression which a positive pole exerts on substitution in a ring that has resonance.

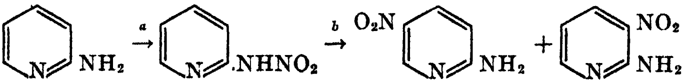
The Ammono-aldehyde System.—Chichibabin,[44] in 1914, discovered that the reaction of sodium amide with pyridine in toluene at 120 to 126° for several hours gives aminopyridine. The process goes in steps, separable at lower temperature; the first is addition across the —C=N— bond, and the second is elimination of sodium hydride. With two equivalents of sodamide, the 2,6-diamino compound is formed. The reaction is



a +$NaNH_2$. b −NaH.

general. Sodium amides of mono alkyl or aryl amines may be used. Alpha substitution occurs almost to the exclusion of the gamma product as long as there is an open position. When forced into the 4-position as in the case of α,α′-lutidine,[45] the reaction is slow and the yield is small.

This reaction is important, because the amino group renders the pyridine ring open to all the usual substitution reactions found in benzene chemistry. Nitration,[46] for example, proceeds stepwise: first the formation of a nitroamine in the mixture of nitric and sulfuric acid at low temperatures, and second, the rearrangement at about 40° in sulfuric acid, chiefly to the 5- and partially to the 3-position. The process, therefore,



a HNO_3. b Rearrangement.

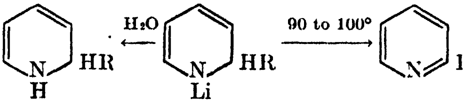
proceeds by an indirect method, and the entering group must be para or ortho to the amino group. Similarly, bromine or iodine can be introduced into the 5-position by addition of these halogens to the α-amino derivative. Subsequently, a nitro group can be made to enter the 3-position. These reactions illustrate the variety of substituted pyridines made available by Chichibabin's amination process. Alkyllithium[47] compounds also add to a C=N group and form an α-alkyl-N-lithio-1,2-dihydropyridine; and again the tendency of the system to revert to the conjugated ring causes lithium hydride to split from the molecule at higher temperature, thereby forming a 2-alkyl-pyridine.

---

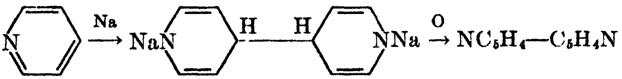
[44] (a) Chichibabin and Zeide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914); *C.A.*, **9**, 1901 (1915); (b) Chichibabin, *Bull. soc. chim.* [5], **3**, 762 (1936); (c) Wibaut and Dingemanse, *Rec. trav. chim.*, **42**, 240 (1923).

[45] Chichibabin, *J. Russ. Phys. Chem. Soc.*, **47**, 835 (1915); *C.A.*, **9**, 2896 (1915).

[46] Chichibabin, *Bull. soc. chim.* [5], **3**, 762 (1936); Chichibabin and Razorenov, *J. Russ. Phys. Chem. Soc.*, **47**, 1286 (1915); *C.A.*, **9**, 3057 (1915); Chichibabin and Menschikow, *Ber.*, **58**, 406 (1925).



Metallic sodium reacts with pyridine as if the latter were an ammono-aldehyde. Sodium attaches itself to the nitrogen atom. Two carbon atoms then join as in a pinacol formation to yield a tetrahydrodipyridyl product. Oxidation with moist air at room temperature or dry air at 90°



completes the formation of γ,γ'-dipyridyl.[48] The method is preparative.

The reaction can produce more than one dipyridyl. If sodium is added to 1 to 5 parts of pyridine and the mixture allowed to stand several days before decomposition with moist air, the product is mostly γ,γ'-dipyridyl; but if the mixture is heated to 114 to 115° for 10 to 16 hr. before decomposition, a variety of products consisting of α,α'-,β,β'-, γ,γ'-, α,β'-, and β,γ'-dipyridyl is produced.[49] This method is the main one for obtaining α,β'-dipyridyl.

The ease of reduction of pyridine systems is undoubtedly caused by the presence of the ammono-aldehyde system and the double bonds conjugated with it. The common reagents are sodium and absolute alcohol[50] and hydrogen over nickel[51] or platinum.[52] When acetic anhydride and zinc[53] are used, the product is N,N'-diacetyltetrahydro-γ,γ'-dipyridyl

---

[47] Ziegler and Zeiser, *Ann.*, **485**, 174 (1921).

[48] Emmert, *Ber.*, **47**, 2598 (1914); **49**, 1060 (1916); **50**, 31 (1917); Emmert and Buchert, *ibid.*, **54**, 204 (1921).

[49] Smith, *J. Am. Chem. Soc.*, **46**, 414 (1924).

[50] Ladenburg, *Ber.*, **17**, 388 (1884); *Ann.*, **247**, 51 (1888); Marvel and Lazier, *Org. Syntheses*, *Coll. Vol.* I, 2d ed., 99.

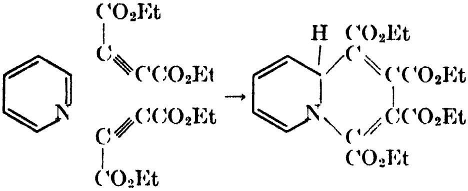
[51] Adkins, Kuick, Farlow, and Wojcik, *J. Am. Chem. Soc.*, **56**, 2425 (1934); Burrows and King, *Jr.*, *ibid.*, **57**, 1789 (1935).

[52] Zelinski and Borisov, *Ber.*, **57**, 150 (1924); Hamilton and Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

[53] Dimroth and Heene, *Ber.*, **54**, 2934 (1921).

(m.p. 124 to 125°). The reaction provides another illustration of the principle that a radical which becomes attached to nitrogen may set free a valence in the gamma-position.[54] Moist air oxidizes the compound to γ,γ'-dipyridyl.

The ammono-aldehyde group will also condense with 2 molecules of ethyl acetylenedicarboxylate to yield a ethyl quinolizine-1,2,3,4-tetracarboxylate.[55]



The influence of the CN group extends also to the behavior of the groups attached to the ring, as will be made evident in later portions of this chapter.

Reactions Dependent on Salt Formation.—Pyridine compounds form salts readily with hydrochloric, hydrobromic, nitric, sulfuric, and other acids. , Picric acid yields salts that are valuable for identification. The mercuric chloride, platinic chloride, and gold chloride double salts are sometimes useful for analysis as is also the methiodide. Phenacyl chloride[56a] is of limited use in this respect. Many salts are helpful in separating mixtures. For example, β-picoline, γ-picoline, and 2,6-lutidine are present in the "β-picoline" fraction (b.p. 140 to 145°) of coal-tar bases. The components of this mixture are separated[56b] by crystallization of the dimercuric chlorides, zinc chlorides, hydrobromides, or better, the oxalates from alchohol.

Pyridine precipitates phenols[57] from aqueous solutions. The more insoluble the substituted phenols, the greater the tendency for the precipitation. The solubility of the phenol decreases as the substituent in the phenol is OH, H, CH_3O, CH_3, $COOCH_3$, Cl, $CO_2C_2H_5$, or NO_2; the precipitating power of the pyridine compound increases in the order, pyridine, α- and β-picoline, and collidine. Ethyl nicotinate is more effective than ethyl picolinate.

Tertiary amines commonly form betaines (inner salts) with chloroacetic acid; and accordingly, pyridine and chloroacetic acid, warmed together on a water bath, yield a brown sirup from which crystals of pyridine betaine hydrochloride separate.[58] The crystals are very soluble in water, difficultly soluble in cold alcohol, but readily soluble in hot alcohol, and insoluble in ether. When heated to 190°, they melt and rapidly evolve carbon dioxide and methyl chloride. Pyridine betaine also forms

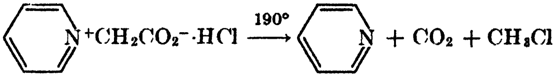
---

[54] DIMROTH and FRISTER, *ibid.*, **55**, 1223 (1922).

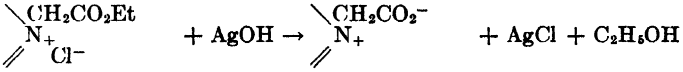
[55] DIELS, ALDER *et al.*, *Ann.*, **510**, 87 (1934).

[56] (*a*) MARVEL, SCOTT, and AMSTUTZ, *J. Am. Chem. Soc.*, **51**, 3638 (1929); (*b*) LIDSTONE, *J. Chem. Soc.*, 241 (1940).

[57] LABES, *Arch. exptl. Path. Pharmakol.*, **190**, 421 (1938); *C.A.*, **33**, 7794 (1939); BERGSTERMANN, NÖCKER, and KRAUSKOPF, *ibid.*, **191**, 55 (1938); *C.A.*, **34**, 4069 (1940).

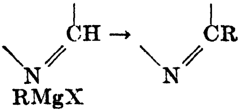


salts with hydrobromic and sulfuric acids. The ethyl ester[59] is prepared from pyridine and ethyl chloroacetate. It forms salts such as the platinic chloride, $(C_9H_{11}NO_2{\cdot}HCl)PtCl_4$; the gold double salt, $(C_9H_{11}NO_2{\cdot}HCl)AuCl_3$, (m.p. 117°); and the mercuric chloride salt, $(C_9H_{11}NO_2{\cdot}HCl)HgCl_2$, (m.p. 124 to 125°). When treated with moist silver oxide, the inner salt is formed.



Trichloroacetic acid[60] forms a salt with pyridine (m.p. 112°), but no betaine. When the salt is treated with mercuric chloride, the trichloroacetic acid is displaced and pyridine mercuric chloride $2C_5H_5N{\cdot}3HgCl_2$ is precipitated.

An addition compound between pyridine and the Grignard reagent exists. Water readily gives back the pyridine. Absence of color with Michler's ketone[61] shows that no uncombined Grignard reagent is present. When heated to 150 to 160° in an autoclave, a 2-alkyl or aryl product, depending on the original Grignard reagent, is formed.[62]



When pyridine is oxidized with a benzene solution of benzoperacid for about 5 hr., and picric acid is then added to the mixture, a precipitate of the picrate of the N-oxide[63] is obtained in almost quantitative yield. The free oxide (m.p. 66 to 68°) can be obtained from the chlorhydrate (picrate with HCl) and ammonia in a freezing mixture, after evaporation of the ethereal extract. The compound is in some respects analogous to the aldonitrones,[64] *i.e.*, to the N-ethers of the oximes, which can also be considered as the oxides of a Schiff base. Table I emphasizes the analogy by a comparison of some addition reactions.[65]

---

[58] v. Gerichten, *Ber.*, **15**, 1251 (1882).

[59] Kruger, *J. prakt. Chem.* [2], **43**, 271 (1891).

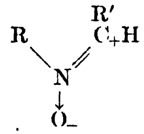
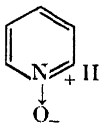
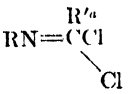
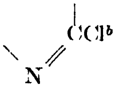
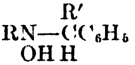
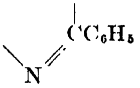
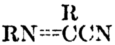
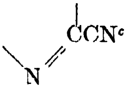
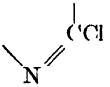
[60] Reitzenstein, *Ann.*, **326**, 305 (1903).

[61] Gilman, Sweeney, and Hech, *J. Am. Chem. Soc.*, **52**, 1604 (1930).

[62] Bergstrom and McAllister, *ibid.*, **52**, 2845 (1930).

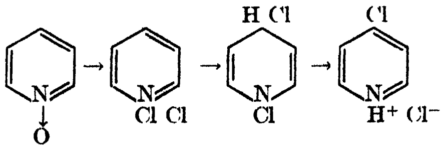
[63] Meisenheimer, *Ber.*, **59**, 1848 (1926).

TABLE I.—COMPARISON OF REACTIONS OF SOME REAGENTS WITH ALDONITRONES AND WITH PYRIDINE N-OXIDES

Reagent		
SO_2Cl_2		
C_6H_5MgBr	 $\underset{\text{OH}}{\text{RN}}—\overset{\text{R}'}{\underset{\text{H}}{\text{C}}}\text{C}_6\text{H}_5$	
KCN	 $\text{RN}{=}\overset{\text{R}}{\text{C}}\text{CN}$	
PCl_5	. . . .	

[a] First stage of reaction. This product is readily hydrolyzed to the amide.
[b] The γ-isomer is also formed.
[c] Reaction inferred by analogy with the behavior of quinoline N-oxide.

The reaction with phosphorus pentachloride is pictured[33] as occurring in the following steps:



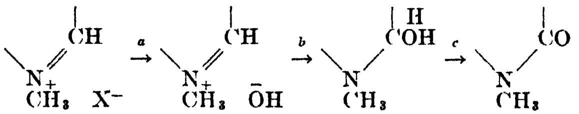
---

[64] The term "nitrones" refers to the class of substances that have the system $\overset{R}{>}C{=}N \rightarrow O$. Pfeiffer [*Ann.*, **411,** 72 (1916)] considered them as having an $=\overset{|}{N}=O$ system, and therefore called them "nitrones analogous to ketones." The similarity suggested by the name is not exact because the C=N ⇉ O acts as a long carbonyl group [Smith, *Chem. Rev.*, **23,** 222 (1938)] rather than as an N=O system. One of the reactive forms is $R\overset{+}{C}H—N(R') \rightarrow \overset{-}{O}$ another is $R\overset{-}{C}H—\overset{++}{N}(R') \rightarrow \overset{-}{O}$.

[65] COLONNA, *Bull. sci. facultà chim. ind. Bologna,* No. 4, 123 (1940); *C.A.*, **34,** 7290 (1940).

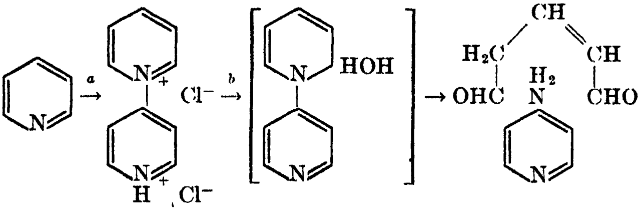
Alkylation[66] of pyridine is effected by heating the alkyl halide salt to 290 to 300° (the Ladenburg reaction). The alkyl group rearranges to the 2- or 4-position. N-Propyl changes partly to isopropyl during this change so that the process does not always give a pure product. If the temperature is too high and the pyridine ring is split, carbon is formed and some alkylbenzene and ammonium halide is produced.

The alkyl pyridinium salt behaves in an interesting manner with alkali. The product appears to be both a quaternary base and a carbinol. The solubility[67] with water in all proportions and the conductivity[68] measurements, particularly when first formed, suggest the ammonium form; but the oxidation with potassium ferricyanide produces a ketone as if the change were that of a carbinol to a ketone.[69]



[a] NaOH. [b] Rearrangement. [c] Oxidation by K_3FeCN_6.

An extremely interesting series of transformations, all in accordance with the behavior of salts, centers around N-pyridylpyridinium chloride.[70] When this compound is heated at 150 to 200° with ammonia, γ-aminopyridine is formed. The reactions, from pyridine as the starting point, are pictured below:



[a] $SOCl_2$ for 3 days at room temperature. This reaction probably proceeds through the intermediate formation of $4\text{-}ClC_5H_4N$, which forms a salt with more pyridine. [b] NH_4OH at 150 to 200°. This reaction probably proceeds by way of the intermediate carbinol, followed by hydrolysis of the amino alcohol.

The pyridinium salt is changed by hydroxyl ion to the pyridinium hydroxide. The tautomeric form of this compound no longer has a purely aromatic character but is a cyclic unsaturated alkanol amine. Heat and hydrolysis open the ring, possibly by way of a Schiff base, $NC_5H_4 \cdot N{=}CHCH{=}CHCH_2CHO$, and form glutaconic aldehyde and γ-aminopyridine. If water is used in place of ammonium hydroxide, the amino group is removed in the process and γ-hydroxypyridine is formed. When the reaction is carried out with potassium phenoxide, the product is γ-phenoxypyridine. If heated on the water bath with aniline, the solution becomes a dark red color, and glutaconic dianil precipitates after acidification. Crystals of 4-(phenylamino)-pyridine are recovered from the residue after the excess aniline is removed by steam distillation.

---

[66] Ladenburg, *Ber.*, **16**, 1410, 2059 (1883); **32**, 42 (1899); Ladenburg and Schrader, *Ann.*, **247**, 22 (1888).

[67] Decker and Kaufmann, *J. prakt. Chem.* [2], **84**, 219 (1911); Decker, *ibid.* [2], **47**, 28 (1893).

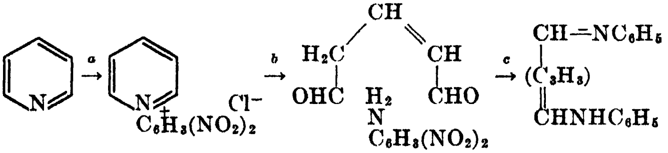
[68] Hantzsch and Kalb, *Ber.*, **32**, 3109 (1889).

[69] Prill and McElvain, *Org. Syntheses, Coll. Vol.* II, 419 (1943).

[70] Koenig and Greiner, *ibid.*, **64**, 1049 (1931).

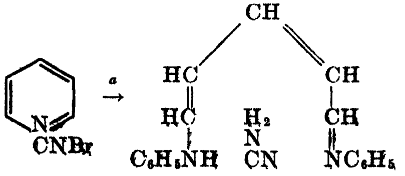
By a similar reaction, 2-chloropyridine is converted to 2-aminopyridine.[71] This reaction was originally carried out with the expectation of effecting a Ladenburg rearrangement to a dipyridyl. The behavior, however, is that of ring degradation.

Ring Opening.—All methods for cleaving the ring focus on the nitrogen atom. Zincke's[72] process, for example, is identical in principle with the synthesis of γ- and α-aminopyridine mentioned in the previous section. 2,4-Dinitrochlorobenzene is warmed on a water bath with pyridine. The pyridinium salt is then treated with sodium hydroxide which causes precipitation of a thick, almost black, precipitate. One gram of the alkali product is then heated with 4 cc. of glacial acetic acid and 4 cc. of concentrated hydrochloric acid. Addition of water precipitates the yellow dinitroaniline. The glutaconic aldehyde is isolated from the mother liquor by addition of aniline and precipitation of the dianilide.



a $C_6H_3(NO_2)_2Cl$. b NaOH, hot HCl-HOAc. c $C_6H_5NH_2$.

The colored product, obtained by the reaction of pyridine with cyanogen bromide,[73] followed by reaction with an aromatic amine, is produced by a parallel process. The red to blue colored product is the same



a $C_6H_5NH_2$.

---

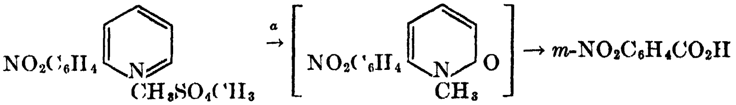
[71] Koller and Ruppersburg, *Monatsh.*, **50**, 436 (1928).

[72] Zincke, Heuser, and Möller, *Ann.*, **333**, 296 (1904); Zincke and Würker, *ibid.*, **338**, 107 (1905); Fischer and Hamer, *J. Chem. Soc.*, 189 (1933).

[73] König, *J. prakt. Chem.* [2], **69**, 105 (1904).

conjugated system of double bonds as is obtained by reaction with dinitrochlorobenzene.

Pyridone has already been described as an unsaturated cyclic amide. It is therefore not surprising that the methosulfate of 2-(*m*-nitrophenyl)-pyridine[74] is oxidized by alkaline permanganate to *m*-nitrobenzoic acid. The steps are indicated below.



[a] NaOH + $KMnO_4$.

In general, acid permanganate oxidizes the aromatic ring of a phenyl-pyridine system, neutral or alkaline permanganate oxidizes the pyridine part.[75] These differences in stability accord with the view that in acid solution the pyridine ring benefits from the protection given by a positive pole while in alkaline medium it has more susceptibility because of the presence of an aldehyde-like function.

Vigorous reduction opens the ring. Hydriodic acid[76] at 300° in a sealed tube splits pyridine into pentane and ammonia. Hydrogen and catalytic nickel at 180° yield amylamine,[77] and at 220° they yield pentane and ammonia. Vigorous treatment[78] at 50 to 100 atm. of hydrogen and 500° in an autoclave (Berginization) breaks the ring into fragments, which vary from methane to pentane, unsaturated hydrocarbons, many amines and nitriles, in addition to some piperidine and dipyridyl.

Ring opening can also be effected by the conventional series of reactions which consists of reduction of the ring to a piperidine, formation of the N-benzoyl derivative,[79] and treatment with phosphorus pentabromide or chloride. This reaction is the same as that already described for ring opening of pyrroles and indoles. It is the best method for preparation of pentamethylene dibromide.

The process of exhaustive methylation will also open the ring.

Aromatic Properties.—So much does the chemistry of nitrogen dominate the reactions of pyridine that the purely aromatic character of this compound may easily be overlooked. Yet the resonance,[80] measured by the difference in heats of formation between the observed amount and that calculated from the values for separated double-bond systems, shows (Table II) that pyridine has more resonance even than benzene.

---

[74] Forsyth and Pyman, *J. Chem. Soc.*, 2912 (1926).

[75] Chichibabin, *Ber.*, **37**, 1373 (1904).

[76] Hofmann, *ibid.*, **16**, 590 (1880).

[77] Sabatier and Senderens, *Compt. rend.*, **144**, 784 (1907).

[78] Thate, *Rec. trav. chim.*, **50**, 77 (1931). *Cf.* Sadikov and Mikhailov, *J. Russ. Phys. Chem. Soc.*, **58**, 527 (1927); *C.A.*, **21**, 3364 (1927).

[79] v. Braun, *Org. Syntheses*, *Coll. Vol.* I, 2d ed., 428 (1941).

[80] Pauling and Sherman, *J. Chem. Phys.*, **1**, 606 (1933); Pauling, "Nature of the Chemical Bond," p. 136, Cornell University Press, Ithaca, N. Y., 1940.

TABLE II.—RESONANCE ENERGY OF VARIOUS MONOCYCLIC COMPOUNDS

	Kg.-cal.
Furan	23
Thiophene	31
Pyrrole	31
Benzene	39
Pyridine	43

This high degree of conjugation has unquestionably a great influence on the reactions of pyridine and of pyridine derivatives. It is responsible also for the fact that all the reactions that might be predicted of an ammono aldehyde are not found.

PYRIDINE COMPOUNDS

Methods for the preparation of many pyridine compounds have been discussed already and need not be restated in detail here. Moreover, the properties of the compounds and of substituents in the ring are dominated by the position of the groups relative to the C=N bond in the ring. The influence of such a system in the ring has already been discussed at length. The examples given in this section extend these observations.

Pyridine (m.p. −42°,[81] b.p. 115.3°) is a liquid with a penetrating and unpleasant odor. Its density is $.97721^{25}_{4}$. With water, it forms a mixture of maximum density (1.00347) at 18 mole per cent. The large amount of contraction and evolution of heat when mixed with water suggests that a hydrate of pyridine forms. The liquid is dried with solid potassium hydroxide,[81] barium oxide, calcium sulfate[82] (Drierite), or phosphorus pentoxide and is extremely hygroscopic. It forms constant boiling mixtures with 3 moles of water[83] (b.p. 92 to 93°), with formic acid, and with acetic acid.[84]

Pyridine is extensively used as a catalyst or as a solvent to promote organic reactions. Eight drops of pyridine with 20 g. of benzaldehyde changes the yield of cinnamic acid in the Perkin condensation[85] from 54 and 70 per cent to 85 per cent and produces a better crude product. This catalytic action is found also with other bases such as trimethyl amine, benzylpiperidine, and quinoline. Four cubic centimeters of pyridine per mole of α-naphthyl amine changes the methylation by methyl sulfate from a 51 to a 66 per cent yield.[86] Mutarotation [87] of berylliumbenzoyl camphor is facilitated by the presence of pyridine. The combination of sulfur dioxide with chlorine to give sulfuryl chloride is catalyzed by pyridine[88] as well as by a number of other compounds that possess residual affinity.

---

[81] DUNSTAN and THOLE, *J. Chem. Soc.*, **93**, 561 (1908); HARTLEY, THOMAS, and APPLEBEY, *ibid.*, **93**, 539 (1908).

[82] HAMMOND and WITHROW, *Ind. Eng. Chem.*, **25**, 653, 1112 (1933).

[83] GOLDSCHMIDT and CONSTAN, *Ber.*, **16**, 2976 (1883); BAUD, *Bull. soc. chim.* [4], **5**, 1022 (1909).

[84] GARDNER, *Ber.*, **23**, 1587 (1890).

[85] BACHARACH and BROGAN, *J. Am. Chem. Soc.*, **50**, 3333 (1928); KALNIN, *Helv. Chim. Acta*, **11**, 979 (1928).

As a solvent, pyridine is particularly efficacious in esterifications in which hydrogen chloride is split from the reagents, such as in the acylation or benzoylation[89] of sugars, the acylation of tertiary alcohols, the acylation with acetic anhydride of primary and secondary alcohols (tertiary alcohols are scarcely affected in this case) present in essential oils,[90] or the formation of olefins by splitting hydrogen halide from the molecule. Simultaneous decarboxylation and dehalogenation occur in the preparation of bromoolefins from α,β-dibromo acids[91a] where the effect of pyridine is comparable to that of sodium carbonate. It is a good solvent for the copper sulfate oxidation of benzoin to benzil, because it prevents precipitation of cuprous oxide, is not so volatile as the ammonia in Fehling's solution, and is a partial solvent for benzoin.[91b] ' The bromine addition compound with pyridine is a good agent for mild bromination.

Pyridine is noted for the large number of complexes it forms with metallic salts, some of which are valuable as qualitative tests. For example, cupric thiocyanate is precipitated from aqueous solution by the addition of pyridine. The precipitate $Cu(CNS)_2 \cdot 2C_5H_5N$ makes an emerald-green solution in chloroform. The test is suitable for detection[92] of 1 part of copper in 800,000, 1 of pyridine in 2,000, and 1 of thiocyanate in 50,000. By a similar process, copper cyanate[93] yields a precipitate $Cu(NCO)_2 \cdot 2C_5H_5N$ that makes a sapphire or azure-blue solution in chloroform. One part of cyanate in 20,000 parts of solution can be detected by this method.

Nickel, cobalt, cadmium, zinc, and silver,[94] in addition to copper, form pyridine cyanates that are soluble in chloroform. Measurements of the dissociation pressure and of the volume change during formation, show that the cupric, cobaltous, and nickelous hexapyridine cyanates have lower dissociation pressures and greater shrinkage (by about 1.74 times) than do the corresponding tetrapyridine thiocyanate salts. Both facts indicate greater chemical affinity in the cyanate compounds. Shrinkage is greatest in the case of nickelous compounds and decreasingly less for cobaltous and cupric salts.

---

[86] GERMATH, *J. Am. Chem. Soc.*, **51**, 1555 (1929).

[87] HUGHES, *Nature*, **129**, 316 (1932); LOWRY and TRAILL, *Proc. Roy. Soc.* (*London*), A, **132**, 398 (1931).

[88] DURRANS, *J. Soc. Chem. Ind.*, **45**, 347 T (1926).

[89] DEULOFEU, CATTANEO, and MENDIVETGUA, *J. Chem. Soc.*, 147 (1934).

[90] DALABY and SABETAY, *Bull. soc. chim.* [5], **2**, 1716 (1935); *cf.* SMITH and BRYANT, *J. Am. Chem. Soc.*, **57**, 61 (1935).

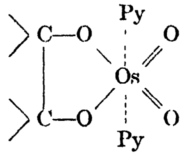
[91] (*a*) FARRELL and BACHMAN, *ibid.*, **57**, 1281 (1935); (*b*) KRAUSE, *Ber.*, **56**, 1801 (1923).

[92] SPACU, *Bul. soc. stiinte Cluj*, **1**, 284 (1922); *C.A.*, **17**, 1772 (1923).

[93] WERNER, *J. Chem. Soc.*, **123**, 2577 (1925).

[94] DAVIS and LOGAN, *J. Am. Chem. Soc.*, **50**, 2493 (1928); **56**, 2153 (1934); DAVIS and OU, *ibid.*, **56**, 1061 (1934).

Complexes with cobalt, nickel, and other metal salts of organic acids such as acetic, mono-, di-, and tri-chloroacetic, cyanoacetic and thiocyanoacetic acids[95] and with fatty acids[96] (acetic to valeric) have also been observed. Complex compounds[97] consisting of osmium tetroxide, olefins, and pyridine are beautiful, crystalline, and stable.



Homologues of Pyridine.—α-,β-, and γ-picolines are obtained largely from coal tar, but may be found also in some petroleum. The chemical properties vary widely. The α- and γ-isomers, which have the methyl group adjacent to the C═N function, condense readily with benzaldehyde[6] under the influence of zinc chloride at 225°. Chloral,[98] so condensed with α- or γ-picoline, becomes an intermediate for the preparation of acids. β-Picoline is unreactive under such conditions and can thus be freed from traces of the other isomers.

$$C_5H_4N{\cdot}CH_3 \xrightarrow{a} C_5H_4N{\cdot}CH_2CH(OH)CCl_3 \xrightarrow{b} C_5H_4N{\cdot}CH_2CH_2CO_2H$$

[a] CCl_3CHO. [b] Dehydration, hydrogenation, hydrolysis.

α-Picoline is very readily chlorinated. β-Picoline, dissolved in hydrochloric acid, must be heated in a sealed tube with bromine at 150° to be converted to β-picolyl bromide, a lachrymator.[99]

The hydrogen atom in α-picoline is replaceable by the lithium[47] in butyllithium and the resulting picolyllithium can react with formaldehyde[22] or benzaldehyde[100] to give 2(2-hydroxyethyl)-pyridine or phenylpicolylcarbinol respectively. By contrast, the corresponding benzyllithium[101] yields *o*-tolylcarbinol, as if the lithium were attached to the ring instead of the side chain.

---

[95] Reitzenstein, Z. *anorg. Chem.*, **32**, 298 (1902).

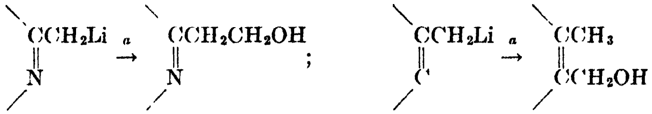
[96] Davis and Logan, *J. Am. Chem. Soc.*, **62**, 1276 (1940).

[97] Criegee, *Z. angew. Chem.*, **51**, 519 (1938).

[98] (*a*) Rabe and Kindler, *Ber.*, **55**, 532 (1922); (*b*) Alberts and Bachman, *J. Am. Chem. Soc.*, **57**, 1284 (1935).

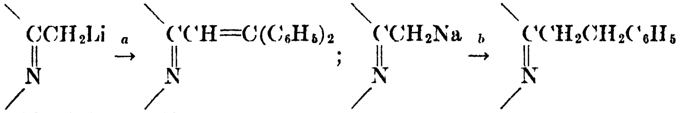
[99] Kahn and Richter, *ibid.*, **57**, 1927 (1935).

[100] Bergmann and Rosenthal, *J. prakt. Chem.* [2], **135**, 277 (1932).



^{a} H_2CO.

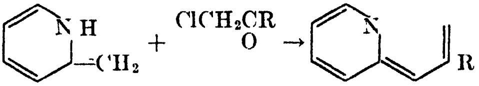
α-Picolyllithium condenses also with benzophenone,[102] but lithium hydroxide is eliminated. The final product is an olefin.



^{a} $(C_6H_5)_2CO$. ^{b} $C_6H_5CH_2Cl$.

α-Picoline is similarly metalated by sodamide and the product then reacts with benzyl[103a] and alkyl halides[103b] to effect chain lengthening. If a ketone is used in place of the halide, the product is a tertiary alcohol. An ester leads to a ketone. This reaction of α-picolin with sodamide can be regarded as typical of an ammono ketone,[104] and not unlike that of methyl ketones such as acetophenone, which are metalated by sodamide and then react with alkyl halides as if the metal were attached to carbon.

α-Picoline might be expected to exist in a tautomeric imine form. The formation of an indolizine[44b] is conveniently interpreted on this basis.



Infrared absorption studies,[105] however, do not encourage the idea that iminization is appreciable.

Pyridylalkenes and -alkynes.—Pyridine compounds with unsaturation in the side chain are prepared by condensing aldehydes with 2- or 4-methyl pyridine. Isoallylpyridine[106] (b.p. 290°) is made from paraldehyde and α-picoline at 250°, and γ-styrylpyridine (stilbazole)[107] (m.p.

---

[101] Gilman and Breuer, *J. Am. Chem. Soc.*, **56**, 1127 (1934).

[102] Ziegler and Zeiser, *Ber.*, **63**, 1847 (1931).

[103] (*a*) Chichibabin, German patent 676,114, May 26 (1939); *C.A.*, **33**, 6345 (1939); German patent 695,640; *C.A.*, **35**, 5647 (1941); (*b*) Chichibabin, *Bull. soc. chim.* [5], **5**, 429, 436 (1938).

[104] Haller, *ibid.* [4], **31**, 1073 (1922); *cf.* Bergstrom and Fernelius, *Chem. Rev.*, **20**, 413 (1937).

[105] Cartwright and Errera, *Compt. rend.*, **200**, 914 (1935).

[106] Ladenburg, *ibid.*, **39**, 2486 (1906); *Ann.*, **247**, 26 (1888).

[107] Friedländer, *Ber.*, **38**, 159 (1905).

TABLE III.—PHYSICAL CONSTANTS OF SOME ALKYLPYRIDINES

Substituent in pyridine	B.p., °C.	Picrate, m.p., °C.	Ref.
None	115.3	165–166	56,108*a*
Picolines			
α-Methyl	128–129	165.5	56,108*a*,*b*
β-Methyl	144.0, 143.8	149–150°	56,108*a*
γ-Methyl	144.6, 145.3	167	56,108*b*
Lutidines			
2,3-Dimethyl-	162–164	187–188	22
2,4-Dimethyl-	157.1, 158	182.5–183	108*a*,*b*,*c*
2,5-Dimethyl-	157	168.5–169.5	108*b*
2,6-Dimethyl	144.4	163	56,108*a* 108*b*
3,4-Dimethyl-	163.5–164.5	163	108*d*
3,5-Dimethyl	171.6	245	108*b*
2-Ethyl	148.7	....	108*e*
3-Ethyl	165–165.3	128–130	108*e*
4-Ethyl	164–165	163	108*f*
Collidines			
4-Methyl-2-ethyl[a]	178.7	115–116	108*g*
4-Methyl-3-ethyl[b]	195–196	148–150	108*h*
2,4,6-Trimethyl[c]	170.3	155.5–156	108*c*
2-Methyl-4-ethyl	177–179	141–142	108*g*
2-Methyl-5-ethyl[d]	173–174	166	108*i*
2-Methyl-6-ethyl	160	127–127.5	108*g*
α-Propyl[e]	166–168	....	25,66
α-Isopropyl	158–159	116	66
2,3,4-Trimethyl	183	179	108*g*
2,3,6-Trimethyl	173–174	143–144	108*g*
2,4,5-Trimethyl	165–168	128–131	108*d*
Parvolines			
1,2,3,4-Tetramethyl	232–234	170–172	108*j*
3,5-Dimethyl-2-ethyl	198–199	149–152	108*k*
2-Butyl	189–192	94	

[a] α-Collidine.

[b] β-Collidine.

[c] *sym*-Collidine.

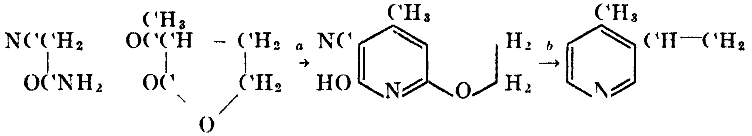
[d] Aldehyde collodine, because it is the principal product from heating aldehyde ammonia.

[e] Conyrine.

[108] (*a*) Heap, Jones, and Speakman, *J. Am. Chem. Soc.*, **43**, 1936 (1921); (*b*) Bratton and Bailey, *ibid.*, **59**, 175 (1937); (*c*) Löffler and Grosse, *Ber.*, **40**, 1325 (1907); (*d*) Ahrens, *ibid.*, **29**, 2996 (1896); (*e*) Seidel and Hazura, *Monatsh.*, **3**, 770 (1882); Stoehr, *J. prakt. Chem.* [2], **45**, 20 (1892); (*f*) Gabriel and Colman, *Ber.*, **35**, 1365 (1902); (*g*) Eckert and Loria, *Monatsh.*, **38**, 225 (1917); (*h*) Koenigs, *Ber.*, **27**, 1501 (1894); (*i*) Fichter and Labhardt, *ibid.*, **49**, 4714 (1909); (*j*) Ahrens, *ibid.*, **28**, 796 (1895); (*k*) Hesekiel, *ibid.*, **18**, 3097 (1885).

127°) is made from a mixture of benzaldehyde and γ-picoline heated with zinc chloride. The process proceeds in steps. If the temperature is reduced to 150°, paraldehyde gives the hydroxy compound[109] $C_5H_4N{\cdot}CH_2{-}CH(OH)CH_3$, which with hydrochloric acid at 185° in a sealed tube gives allylpyridine.

3-*Vinyl-4-methylpyridine.*[110]—Preparation of this compound starts either from ethyl α(β-ethoxyethyl)-acetoacetate (itself derived from ethyl acetoacetate[110] by conventional steps) or from α-acetobutyrolactone. The last method is particularly interesting because it illustrates a way of protecting the side chain by making it part of a dihydrofuran compound.

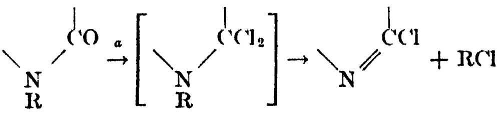


[a] NH₃ to form pyridine compound, but lactone ring simultaneously opens, conc HCl reflux to form furan ring [b] HCl at 150° eliminates the nitrile group and forms two isomers The enolic isomer melts at 250° and gives a positive ferric chloride test, the keto isomer melts at 177.5 to 179° and gives no color with the iron salt Both varieties react with $POCl_3$ to give a trichloro derivative with ring opening H_2 + Pd eliminates the chloro atoms at C_2 and C_6, alcoholic KOH then eliminates HCl to form the vinyl group

Pyridylacetylene.[98b]—This compound is prepared from β-acetylpyridine by chlorination and removal of hydrogen halide.

$$C_5H_4N{\cdot}C(O)CH_3 \xrightarrow{PCl_5} C_5H_4N\ C(Cl){=}CH_2 \xrightarrow[\text{reflux}]{\text{alc KOH}} C_5H_4N{\cdot}C{\equiv}CH$$

Halogen Derivatives.— In addition to the vapor-phase process already described, halogen derivatives may be prepared by (*a*) mercuration of pyridine with mercuric acetate at 170° followed by treatment of the product with salt and then bromine;[111] (*b*) chlorination of pyridones or alkylpyridones with phosphorus pentachloride and phosphorus oxychloride[112] or even with phosgene[113] at elevated temperatures; (*c*) treatment



[a] PCl_5 or $COCl_2$.

of α- or γ-aminopyridine with sodium nitrite in concentrated hydrochloric acid; and (*d*) preparation of a β-halogen compound via the customary diazonium route from a β-aminopyridine.

---

[109] LADENBURG, *Ann.*, **301**, 117 (1898).

[110] STEVENS, BENTEL, and CHAMBERLAIN, *J. Am. Chem. Soc.*, **64**, 1093 (1942).

[111] McCLELAND and WILSON, *J. Chem. Soc.*, 1263, 1497 (1932).

[112] FISCHER, *Ber.*, **32**, 1297 (1899); FARGHER and FURNESS, *J. Chem. Soc.*, **107**, 688 (1915).

[113] BINZ and RÄTH, *Ann.*, **486**, 71 (1931).

TABLE IV.—BROMO DERIVATIVES[42] OF PYRIDINE

-Pyridine	M.p., °C.	B.p., °C.	Pressure, mm.	$HgCl_2$ compound m.p., °C.
2-Bromo-	−40.1[a]	193.4–194	764	184–185°
3-Bromo-	−29.5[a]	173.7–174	762	201.5–202.5
2,6-Dibromo-	118.5–119	249	757.2	
2,5-Dibromo-	93-94	234–235	772	181–182
3,5-Dibromo-	111.5–112	222	755	207–208
2,3,6-Tribromo-	82-83			
2,4,6-Tribromo-	107.5–108.5			
2,3,5-Tribromo-	46	277	772	183-185
3,4,5-Tribromo-	106–107	....	......	207–208
2,3,5,6-Tetrabromo-	103.5–104			
Pentabromo	209.5-210°			

[a] Solidification point.

A halogen atom in the 2- or 4-positions would, if the comparison with an ammono-aldehyde system were exact, behave as an acid chloride or bromide. The resonance in the ring, however, prevents the reactivity of a halogen atom from reaching such extreme limits. 4-Methyl-2,6-dichloropyridine,[114] for example, will not condense with benzene in the presence of aluminum chloride. Nevertheless there are real differences in reactivity according to the position occupied. At C_3, the halogen has the unreactivity associated with aromatic systems; at C_2 and C_4, it has appreciable reactivity and can be ammonlyzed without the aid of catalytic copper. The data in Table V show also that 2,6-dihalo-substituted pyridines have even more reactivity than the 2- or 6-mono compound. The aromatic nature of halogen in the 3-position is further illustrated by the exchange reaction of 3-bromopyridine and *n*-butyllithium which yields 3-pyridyllithium.[115]

$$3\text{-}C_5H_4N{\cdot}Br + n\text{-}C_4H_9Li \rightarrow 3\text{-}C_5H_4N{\cdot}Li + n\text{-}C_4H_9Br$$

Amino Derivatives.—In addition to the amination process of Chichibabin and the reactions shown in Table V, aminopyridine compounds can be prepared by conventional methods from (*a*) amides by the Hofmann reaction; (*b*) acids through the acid chloride, ester, hydrazide, azide, urethane path;[123] and (*c*) nitro derivatives by reduction. The numerous possibilities of reactions from 2-aminopyridine are shown in Fig. 3. An amino group in the 3- or 5-position shows the behavior of an aromatic amine. It can be diazotized, and the diazonium salt will undergo the usual replacement by halogen, nitrile, arsenic acid, or other group and will couple with phenols and amines. The same attempts with 2- or 4-aminopyridine usually lead to hydrolysis. In concentrated hydrochloric or hydrofluoric acid, the amino group is sometimes converted by sodium nitrite into an α-chloro or fluoro compound, as in 2-amino-5-nitropyridine

---

[114] OCHIAI, *J. Pharm. Soc. Japan*, **60**, 164 (1940); *C.A.*, **34**, 5449 (1940).

[115] GILMAN and SPATZ, *J. Am. Chem. Soc.*, **62**, 446 (1940).

TABLE V.—REACTIVITY OF HALOGEN ATOMS ATTACHED TO THE PYRIDINE NUCLEUS

Pyridine substituents	Reagent	Temperature	Product-Pyridine	Ref.
2-Bromo..........	aq. NH_3	180–200°	2-Amino	42,116
3-Bromo..........	aq. NH_3	180–200°	3-Bromo	116
3-Bromo..........	aq. NH_3CuSO_4	200°	3-Amino	116
4-Bromo..........	aq. NH_3CuSO_4	200°	4-Amino	116
2,3,5-Trichloro. ..	aq. NH_3	180°	2-Amino-3,5-dichloro	117
2,3,5-Tribromo.	aq. NH_3	180–190°	2-Amino-3,5-dibromo	118
3,4,5-Tribromo. ...	aq. NH_3	....	4-Amino-3,5-dibromo	42,116
2-Bromo..........	Cu powder	Heat	2,2′-Dipyridyl	116
2-Bromo..........	Mg	Room	2-Pyridylmagnesium bromide	119
2-Bromo..........	CuCN	Heat	2-Cyano	116
3-Bromo..........	CuCN	165–170°	3-Cyano	116
2-Bromo..........	Piperidine	145° 10 hr.	2-Piperidino	120
2-Bromo..........	Aniline	Below 200°	2-Anilino	120
2,6-Dibromo.......	NaOH	90°	2-Ethoxy-6-bromo and 2-Hydroxy-6-bromo	116
2,6-Dibromo.	NaOEt	160°	2,6-Diethoxy	116
2,6-Dibromo.	aq. NH_3	180–200°	2-Amino-6-bromo	42,116
3,5-Dibromo.	aq. NH_3·$CuSO_4$	200°	3,5-Diamino	116
2-Amino-6-bromo. .	NaOH in EtOH	160°	2-Amino-6-ethoxy	116
2,4,6-Tribromo.....	Aq. NH_3	200°	2,6-Diamino-4-bromo	121
2,6-Dibromo.......	70% H_2SO_4, 80% H_3PO_4, 60% HOAc or 60% HCOOH	160°	2-Bromo-6-hydroxy	122

---

[116] (*a*) DEN HERTOG and WIBAUT, *Rec. trav. chim.*, **55**, 122 (1936); (*b*) MCELVAIN and GOESE, *J. Am. Chem. Soc.*, **63**, 2283 (1941); CRAIG, *ibid.*, **56**, 232 (1934).

[117] SELL, *J. Chem. Soc.*, **93**, 2001 (1908).

[118] WIBAUT and KRAAY, *Rec. trav. chim.*, **42**, 1084 (1923).

[119] OVERHOFF and PROOST, *ibid.*, **57**, 179 (1938).

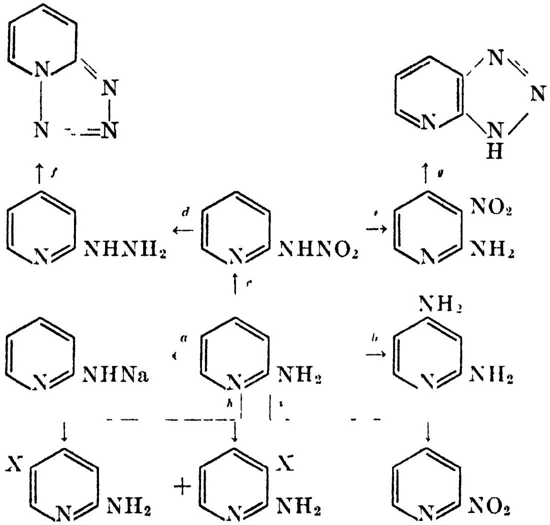
[120] WIBAUT and TILMAN, *ibid.*, **52**, 987 (1933).

[121] WIBAUT, BICKEL, and BRANDON, *ibid.*, **58**, 1124 (1939).

[122] WIBAUT, HAAYMAN, and VAN DIJK, *ibid.*, **59**, 202 (1940).

[123] MEYER and STEFFANS, *Monatsh.*, **34**, 517 (1913).

to 2-chloro-5-nitropyridine,[124] and much pyridone. A similar replacement by bromine is not possible because concentrated hydrobromic reacts with nitrous acid.



[a] This reaction occurs during the amination process, either by metalation of the aminopyridine by sodium hydride or by sodamide. [b] This reaction also occurs during the formation of 2-aminopyridine. [c] HNO_3 in H_2SO_4 below 40°. [d] Reduction with zinc dust and alkali. [e] Heat above 40° causes rearrangement to the 3- and the 5-nitro compounds. [f] HNO_2. [g] Sn + HCl followed by HNO_2. [h] Chlorination, bromination, or sulfonation. [i] $(NH_4)_2S_2O_4$.

FIG. 3.—Some reactions of 2-aminopyridine and of products derived therefrom.

The more stable sodium diazotate may be employed with advantage in some diazo reactions. Acidification of a concentrated solution of the

$$C_5H_4N{\cdot}NH_2 + C_5H_{11}ONO + NaOEt \rightarrow C_5H_4N{\cdot}N_2ONa + C_5H_{11}OH + EtOH$$

diazotate with acetic acid gives pyridone. Careful acidification of a solution that contains potassium iodide yields 2-iodopyridine. Coupling[125] occurs with α-naphthol, resorcinol, and 2,6-diaminopyridine. The coupling rate is accelerated and in some cases is possible only when a slow stream of carbon dioxide is passed through the solution. The simple azo dyes so prepared are not very stable.

α-Aminopyridine undergoes phenylation to give phenyl α-pyridyl amine[126] by an Ullmann synthesis between 2-aminopyridine and bromo- or iodo-benzene with potassium carbonate and metallic copper.

---

[124] CHICHIBABIN and RJAZANCEV, *J. Russ. Phys. Chem. Soc.*, **46**, 1236 (1914); **46**, 1581 (1914); *C.A.*, **10**, 2898 (1916); *Cf.* Ref. 46*a*.

[125] CHICHIBABIN, *J. Russ. Phys. Chem. Soc.*, **50**, 512 (1920); *C.A.*, **18**, 1496 (1924).

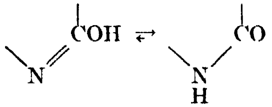
[126] CHICHIBABIN, *J. Russ. Phys. Chem. Soc.*, **50**, 497 (1920); *C.A.*, **18**, 1495 (1924).

Dipyridyl[127] and tripyridyl[7c] are formed when the monoaminopyridine hydrate is heated.

Nitro Compounds.—α-Pyridylnitramine, $C_5H_5N.NHNO_2$(m.p. 184°), is a very important compound in syntheses[46] (see page 194). It is but little soluble in concentrated mineral acids and therefore has no basic properties. It is a strong enough acid, however, to liberate carbon dioxide from carbonates and to dissolve in moderately dilute alkali. It forms a crystalline potassium salt.

2-Nitropyridine[128] (m.p. 68°) can be obtained from 2-aminopyridine by oxidation with ammonium persulfate, hydrogen peroxide, and sulfuric acid. It is also obtained as a by-product in the preparation of 3-nitropyridine[129] (m.p. 41°) when a solution of pyridine in 100 per cent sulfuric acid is added to fused sodium-potassium nitrate at temperature of 300 to 450°. At the higher temperature, the 2-nitro compound is the sole product, although in slight yield (2.5 per cent).

Hydroxypyridines and Pyridones.—Hydroxyl groups attached to the pyridine ring have widely different behaviors, depending on their position. Those in the β-position, for example, are true phenols. They give a ferric chloride test, are weakly acidic (also weak bases), and have an absorption spectra[130] similar to that expected of phenols in general. The α- and γ-hydroxy compounds, on the other hand, show evidence of existing in a tautomeric state with a cyclic amide.



When treated with diazomethane, the methylated product is basic and is demethylated by the conventional reagent (HI) for methoxy groups. The ether, moreover, is identical with that which results from reaction between α-chloropyridine and sodium methoxide. The pyridone silver salt and alkyl iodide yield also the alkoxy compound. On the other hand, if the hydroxy-compound is heated with methyl iodide the nitrogen derivative, $-NCH_3$, is known to be formed, since the remnants of oxidation show that the methyl group is attached to the nitrogen atom.

---

[127] CHICHIBABIN and WOROBIEFF, *J. Russ. Phys. Chem. Soc.*, **50,** 522 (1920); *C.A.*, **18,** 1496 (1924); CHICHIBABIN, *Ber.*, **61,** 199 (1928).

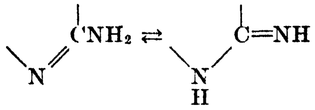
[128] KIRPAL and BÖHM, *ibid.*, **64,** 767 (1931).

[129] DEN HERTOG, JR., and OVERHOFF, *Rec. trav. chim.*, **49,** 552 (1930).

[130] BAKER and BALY, *J. Chem. Soc.*, **91,** 1122 (1907).

[131] (*a*) V. PECHMANN and BALTZER, *Ber.*, **24,** 3144 (1891); V. PECHMANN, *ibid.*, **28,** 1624 (1895); (*b*) CHICHIBABIN, KONOWALOWA, and KONOWALOWA, *ibid.*, **54,** 814 (1921).

Aminopyridine[131b] shows a parallel tautomerism. The action of



sodamide and then methyl iodide in ether solution, for example, introduces a methyl on the amino group, $C_5H_4N\cdot NHCH_3$. Methyl iodide alone, however, forms the salt with the ring nitrogen, $NH_2\cdot C_5H_4N\cdot MeI$, and this compound on treatment with silver oxide yields the N-methyl-α-pyridoneimide. The imide forms a benzoyl derivative (Schotten-Baumann reaction), reacts with phenylisocyanate, and hydrolyzes under the influence of hydrochloric acid at 125° to N-methylpyridone.

Pyridine-2-aldehyde (*b.p.* 181°/760 *mm.*).—This analogue of benzaldehyde can be prepared by condensing α-picoline with benzaldehyde, ozonizing the α-stilbazole produced, and separating the benzaldehyde by steam distillation.[132]

Formation of aldehyde by chlorination and hydrolysis, as in the aromatic series, can also be realized, but the process must be regulated carefully. For example, α-picoline, in contrast to pyridine, is attacked very readily by chlorine in aqueous solution and changes to 3,4,5,ωωω-hexachloro- and 3,5,ωωω-pentachloro-α-picoline.[117] If the picoline is dissolved in glacial acetic acid heavily buffered with sodium acetate, the process can be regulated to give ω-trichloropicoline[133] in a yield of 28 per cent. The trichloro compound can be (*a*) hydrolyzed by aqueous 30 per cent sulfuric acid to picolinic acid or (*b*) reduced by stannous chloride to ω-dichloropicoline, which in turn is hydrolyzed by the acid solution to pyridine-2-aldehyde.

Rosenmund's method for the preparation of aldehydes fails in the case of a simple pyridine acid chloride but succeeds with a substituted compound.[134a]

$$4,6\text{-}Cl_2\cdot C_5H_2N\cdot COCl\text{-}(2) \xrightarrow{a} 4,6\text{-}Cl_2\cdot C_5H_2N\cdot CHO$$

[a] H_2 and Pt in xylene at 150 to 160°.

Small yields of aldehyde are obtained by oxidation of picoline with selenium dioxide.[134b] (*Cf.* page 277.)

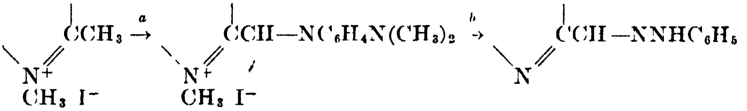
Pyridine-2-aldehyde is characterized by the hydrazone (m.p. 180 to 182°), the 2,4-dinitrophenylhydrazone (m.p. 213°), and the bisulphite addition compound which sublimes at about 160°. The phenylhydrazone of the aldehyde may be secured indirectly by condensing α-picoline methiodide with *p*-nitrosodimethylaniline and hydrolyzing the anil in the presence of phenylhydrazine.[135] The methyl iodide is then removed by heating in a high vacuum. The hydrazone can be split into its components by warm mineral acid.

---

[132] HARRIES and LENART, *Ann.*, **410**, 95 (1915).

[133] DYSON and HAMMICK, *J. Chem. Soc.*, 781 (1939).

[134] (*a*) GRAF and WEINBERG, *J. prakt. Chem.*, **134**, 177 (1932); (*b*) BORSCHE and HARTMANN, *Ber.*, **73**, 839 (1940).



[a] $ONC_6H_4N(CH_3)_2$. [b] Dilute HCl + $C_6H_5NHNH_2$, heat in vacuum to remove methyl iodide.

Pyridine Ketones.—Since direct acetylation of pyridine does not occur, the 3-acetyl derivative is obtained by an indirect method.[136] Ethyl nicotinate, when condensed (by NaOEt) with ethyl acetate, yields ethyl nicotinoacetate which can be isolated if desired as the hydrochloride (m.p. 156 to 157.5°). When this compound is refluxed in 10 per cent hydrochloric acid, the β-acetylpyridine is formed.

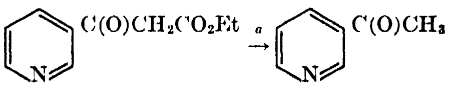
TABLE VI.—PHYSICAL PROPERTIES OF PYRIDINE CARBOXYLIC ACID

Position of carboxyl group or groups	Common name	M.p., °C.	Ref.
2-	Picolinic	133[a]	133,131
3-	Nicotinic	230–232	161
4-	Isonicotinic	305–307	66
2,3-	Quinolinic	230 d.[b]	138*a*
2,4-	Lutidinic	248–250	138*b*
2,5-	Isocinchomeronic	256–258 d.	138*c*
3,4-	Cinchomeronic	264–265	106*d*
3,5-	Dinicotinic	323	106*g*

[a] The melting point of the hydrochloride salt is 228 to 230° if heated at the normal rate but falls to 210 to 212° if the rate of temperature increase near the melting point is 1° every 5 min.

[b] The amide melts at 209°.

[138] (*a*) LINSTEAD, NOBLE, and WRIGHT, *J. Chem. Soc.*, 911 (1937); (*b*) MEYER and TROPSCH, *Monatsh.*, **35**, 189 (1914); (*c*) JACOBS and CRAIG, *J. Biol. Chem.*, **124**, 659 (1938).



[a] Hydrolysis with 10 per cent HCl.

Pyridine carboxylic acids are important because they serve as reference points in problems of structures. They are commonly prepared by oxidation with permanganate. Picolinic acid,[137] for example, is obtained in 50 to 51 per cent yield from α-picolin.

---

[135] KAUFMANN and VALLETTE, *ibid.*, **45**, 1736 (1912); **46**, 49 (1913).

[136] HURD and WEBB, *J. Am. Chem. Soc.*, **49**, 551 (1929); STRONG and MCELVAIN, *ibid.*, **55**, 816 (1933).

[137] SINGER and MCELVAIN, *Org. Syntheses*, **20**, 79 (1940).

Since 2- or 4-carboxylic acids are α- or γ-ammonoaldehydo acids, the carboxyl groups are removed by heat much more readily than those in the 3- or 5-position. 2,3,5,6-Tetracarboxylic acid, for example, loses two carboxyl groups in boiling acetic acid.[139] The two β-carboxyl groups are unchanged even at 285°. The 2,3-diacid melts with decomposition at 190°, solidifies, and then melts without further decomposition at 230°. 3-Acetyl-4-methylpyridine-2,6-dicarboxylic acid[10] loses one carboxyl group after many hours in boiling acetic acid. The second carboxyl group is lost at about 260°.

An aqueous solution of pyridine α-carboxylic acid gives a red to yellow color with ferrous sulfate,[140] probably because of a metal complex. The β- and γ-acid give no color. This test is regularly employed to indicate an α-carboxylic acid.

β-Pyridine carboxylic acid is commonly known as *nicotinic acid* because it is the acid obtained by oxidation of nicotine with nitric acid. The acid is one of the components of the mixture that was originally called vitamin B. The complex nature of this growth factor was recognized when Goldberger[111] and coworkers of the U. S. Public Health Service showed that pellagra was due to a deficiency in the diet of one of the components of this mixture. This necessary portion was accordingly called vitamin B_2 and later shown to be nicotinic acid. 2,6-Dimethyl-3,-5-dicarboxylic acid, 3,5-pyridinedicarboxylic acid, 3-pyridine-N-diethylcarboxamide (coramine), and 3-methylpyridine are less effective than nicotinic acid in controlling the disease.

Nicotinic acid is widely distributed in nature. Liver-extract powder, yeast-extract powder, the aqueous concentrate of rice-polish extract, wheat-germ powder, and cow's milk contain 1.15, 2.52, 2.84, 0.15, and 0.13 mg. per g., respectively.[142] The amount present in whole-wheat flour is around 9.5 mg. per g. The customary test for the presence of this vitamin is the cyanogen bromide–aniline procedure (page 200). This test of course is general for many pyridine compounds, although not for vitamin B_6.

The acid is prepared in commercial quantities by oxidation of nicotine or alkyl β-substituted pyridine compounds. It can also be prepared by hydrolysis of the nitrile[116b] and by partial decomposition of quinolinic acid.

The diethylamide of nicotinic acid is called *coramine* and is used in medicine as a respiratory and cardiac stimulant.[141]

---

[139] SKRAUP, *Monatsh.*, **2**, 147 (1881).

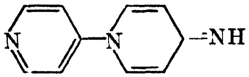
[140] SKRAUP, *ibid.*, **7**, 210 (1886), *cf.* LEY, SCHWARTE, and MÜNNICH, *Ber.*, **57**, 349 (1924).

[141] GOODMAN and GILMAN, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

[142] MELNICK, OSER, and SIEGEL, *Ind. Eng. Chem., Anal. Ed.*, **13**, 879 (1941).

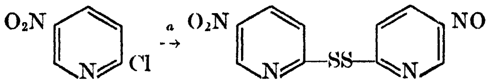
Pyridine Sulfonic Acids and Derivatives.—Apart from direct sulfonation, which takes place with difficulty, the β-sulfonic acid can be prepared by converting a β-halopyridine to the thio derivative (by KSH) and thence to the acid (by H_2O_2). The compound is soluble in water and alcohol but not in benzene. The formula is probably best represented as a zwitterion, $H\overset{+}{N}C_5H_4{\cdot}SO_3^-$.

An α- or γ-sulfonic acid can be prepared by converting (P_2S_5) a pyridone to the thio derivative and then oxidizing[143] (HNO_3) to the sulfonic acid. Efforts to convert (PCl_5, NH_3) the γ-acid to the amide in order to obtain a compound of the sulfanilamide type with nitrogen in the ring leads to the formation of 1-(4′-pyridyl)pyridine-4-imine,[144]



presumably by replacement of a sulfonic by an amino group.

Conversion of a mercaptan to a sulfonic acid by oxidation does not always occur, as witnessed by formation of the dinitro disulfide[145] in the following sequence of reactions:



a KSH and heat, H_2O_2.

Di- and Poly-pyridyls.—Besides the preparation of γγ′- and other dipyridyls from sodium and pyridine, already described, the two pyridine nuclei can be linked by the customary pyrolytic method employed with aromatic compounds. For example, pyridine, passed through a red-hot tube[146] or over nickel[147a] at 320°, or heated with iodine[147b] at 320° (iodine aids formation of diphenyl from benzene over hot nickel) yields dipyridyl. Formation of 2,2′-dipyridyls is favored by heating pyridine with anhydrous ferric chloride[148] at 300°, possibly because the two products, *i.e.*, the

$$2C_5H_5N + 2FeCl_3 \rightarrow (-C_5H_4N)_2 + 2HCl + FeCl_2$$

dipyridyl and the ferrous chloride, form a complex with each other.

These salts have the composition (Fe dipyr.$_3$)$Br_2{\cdot}6H_2O$. Ferrous sulfate and nickelous salts also form complexes. The structure of these colored complexes is indicated by the work of Werner,[149] who separated the ferrous compound into its optical isomerides by means of the tartrate salt. The molecular assymmetry is caused by the spatial arrangement of structurally identical groups in the coordinate positions (octahedral spacing) about the central atom. Ethylene diamine gives a similar result.

---

[143] Marckwald, Klemm, and Trabert, *Ber.*, **33**, 1556 (1900).

[144] King and Ware, *J. Chem. Soc.*, 873 (1939).

[145] Räth, *Ann.*, **487**, 105 (1931).

[146] Meyer and Hofmann-Meyer, *J. prakt. Chem.* [2], **102**, 287 (1921).

[147] (*a*) Wibaut and Wellink, Jr., *Rec. trav. chim.*, **50**, 287 (1931); (*b*) Willink, Jr., and Wibaut, *ibid.*, **54**, 275 (1935).

[148] Morgan and Burstall, *J. Chem. Soc.*, 20 (1932); Hein and Ritter, *Ber.*, **61**, 1790 (1928); Hein and Schwedler, *ibid.*, **68**, 681 (1935).

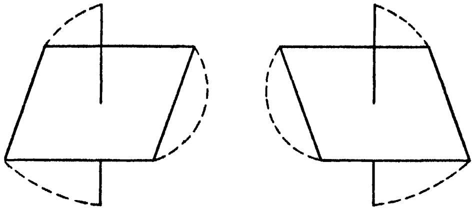
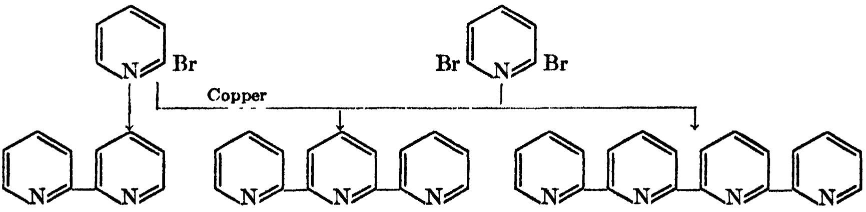


TABLE VII.—PHYSICAL PROPERTIES OF THE DIPYRIDYLS

Position	M.p., °C.	B.p., °C.	Picrate m.p., °C.	Soln. in H_2O	Ref.
αα′	70	272.5	155	Sl. sol.	49,148,150
αβ′	Liquid	287–289	149.5	Insol.	49
αγ′	Liquid	280–282	208	Insol.	49
ββ′	68	291–292	232		49
βγ′	62	297	215	Very sol. cold Sl. sol. hot	49
γγ′	114	305	262	Sol. hot	44c,49

Preparation of 2,2′-dipyridyl by the ferric chloride method is accompanied by formation of considerable quantities of polypyridyls linked together in the alpha positions. These higher molecular weight compounds, as well as 2,2′-dipyridyl itself, can also be prepared by heating 2-bromo-substituted pyridines with copper powder in *p*-cymene or, better, in diphenyl[150] as a solvent. Penta- and hexa-pyridyls can thus be made. All form complexes with ferrous salts.



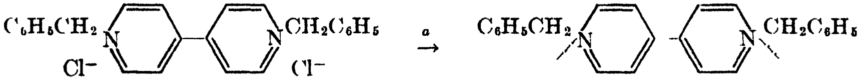
6,6′-Dibromo-2,2′-dipyridyl is prepared by bromination of dipyridyl vapor at 500°. It is converted to the diamino compound by ammonium hydroxide at 200 to 210°. The 6,6′-dimethyl compound can be prepared from α-picoline and ferric chloride at 350°, and this product in turn is oxidized by selenium dioxide to the dicarboxylic acid. All these substituted α,α'-dipyridyls show a marked decline in coordinating power with ferrous chloride, a fact that may be attributed to a screening effect of the group adjacent to the nitrogen atom.

---

[149] WERNER, *ibid.*, **45**, 121, 433 (1912).

[150] WIBAUT and OVERHOFF, *Rec. trav. chim.*, **47**, 761 (1928); BURSTALL, *J. Chem. Soc.*, **1662** (1938).

γ,γ'-Dipyridyl unites with benzyl chloride by a sealed-tube reaction to form N,N′-dibenzyl-γ,γ'-dipyridinium chloride. Sodium, zinc, or magnesium in water converts this product to a blue monohalide or radical; sodium amalgam in methanol removes both halogen atoms and forms the colored biradical.[151]



a. NaHg.

Nicotine, $C_{10}H_{14}N_2$, is the chief alkaloid[152] in the tobacco plant. It is a water-soluble liquid that boils at 246.7°/745 mm., does not solidify at −79°, has a density (near 1.0107 at 20°) greater than that of water, possesses levorotation, and turns brown on exposure to air. It is a feeble base and forms salts with two equivalents of alkyl halide. Its solubility relations with water are interesting, for it is one of the compounds for which a closed temperature-solubility curve[153] is known. The upper critical solution temperature is 210°; the lower is 60°. The phenomenon is related to hydrate formation. At the higher temperature, the hydrate dissociates to nicotine and water.[154]

Nicotine is named after Nicot, the French ambassador to Portugal, who, in 1550, sent tobacco seed to Paris. Although the alkaloid was known [155] by 1571, it was not until 1828 that the material was purified and its position as the first known liquid alkaloid established. The correct formula was determined in 1843 and the first synthesis carried out in 1904 by Pictet.

The alkaloid[152] occurs throughout the tobacco plant, but the percentage is greatest in growing leaves and in the medial zone of the long axis of the leaf. Top leaves contain more than bottom ones. It is isolated by treatment of the leaves or refuse with alkali or lime followed by steam distillation. The compound is without therapeutic value, although shortly after its discovery the plant was widely cultivated in the belief that it was a medicinal herb.[155] The reputation as a medicine was probably based considerably on the odor.

---

[151] Schwab, Schwab-Agallidis, and Agliardi, *Ber.*, **73**, 279 (1940).

[152] Jackson, *Chem. Rev.*, **29**, 123 (1941); Henry, "Plant Alkaloids," The Blakiston Company, Philadelphia, 1939.

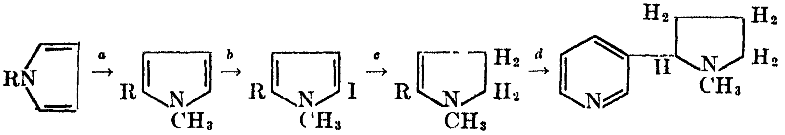
[153] Hudson, *Z. physik. Chem.*, **47**, 113 (1904).

[154] Tsakalotos, *Bull. soc. chim.* [4], **5**, 397 (1909).

[155] Fletcher, Jr., *J. Chem. Education*, **18**, 303 (1941).

Nicotine is one of the most toxic of all drugs and acts with a rapidity comparable to cyanide. Changes caused in the body are complex and often unpredictable, since both stimulant and depressive phases are present.[141] The antidote is another alkaloid of *Nasturtium officinali.* It has not yet been established that moderate use of tobacco is deleterious, although the acute effects observed in the novice are almost entirely due to the nicotine content.

Pictet's synthesis[156] is an excellent application of the principles of pyrrole chemistry. β-Aminopyridine, itself prepared by the Hofmann reaction from nicotinamide, is distilled with mucic acid and the N-pyridylpyrrole product rearranged by heat to the α-isomer. The remaining steps consist of methylation, iodination to obtain a mono-substitution product which is easily reduced, bromination and reduction to obtain the tetrahydro product, and resolution of the optical isomer.



R = C_5H_4N.

[a] Thermal rearrangement, KOH, CH_3I. [b] I_2 in alkaline solution. [c] Sn + HCl. [d] Br_2, Sn + HCl, resolution with *d*-tartaric acid.

Nicotine is oxidized to nicotinic acid by chromic acid,[157] potassium permanganate,[158] or more commonly by nitric acid.[159] A pyrazole by-product (page 440) is formed with the last reagent. Dehydrogenation over 30 per cent platinized asbestos[160] at 320° or in boiling toluene with sulfur[161] gives 3,2′-nicotyrine. Reduction by sodium or hydrogen over platinum oxide–platinum black gives hexahydro- and octahydro-nicotine, in varying amounts.[162] The last product is formed by opening of the pyrrolidine ring.

Nicotine[152] is characterized by the picrate, which is obtained by the addition of a 10 per cent hydrochloric acid solution to a well cooled solution of picric acid. The yellow amorphous precipitate changes to crystals that have a characteristic appearance and are readily detected on a microscale.

---

[156] Pictet and Rotscky, *Ber.*, **37**, 1225 (1904).

[157] Huber, *ibid.*, **3**, 849 (1870); *Ann.*, **141**, 271 (1863).

[158] Oliveri, *Gazz. chim. ital.*, **25**, 59 (1895).

[159] McElvain, *Org. Syntheses, Coll. Vol.* I, 2d ed., 385 (1941).

[160] Wibaut and Overhoff, *Rec. trav. chim.*, **47**, 935 (1928).

[161] Morton and Horvitz, *J. Am. Chem. Soc.*, **57**, 1860 (1935).

[162] Windus and Marvel, *ibid.*, **52**, 2543 (1930).

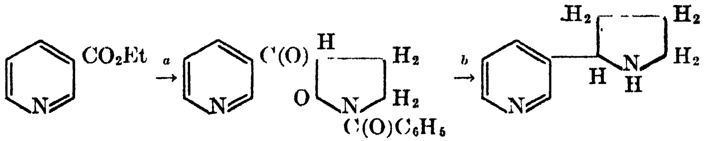
Metallic salts such as mercuric chloride form addition compounds. Table VIII lists the lowest quantity of reagent and the minimum quantity of nicotine that can be detected.

TABLE VIII.—SENSITIVITY OF NICOTINE TO TESTS BY VARIOUS REAGENTS

Reagent	Min. reagent strength parts per 100	Least quant. of nicotine detectable, mg.
$HgCl_2$	1:100	.01
Potassium mercuric iodide	1:500	.002
CdI	1:1,000	.001
$CdBr_2$	1:400	.005
$CdCl_2$	1:100	.02
Picric acid	1:100,000	.001
Picrolonic acid	1:100	.005

The alkaloids, nicotoine, $C_8H_{11}N$, nicotelline, $C_{10}H_8N_2$, isonicoteine, $C_{10}H_{12}N_2$, nicotimine, $C_{10}H_{14}N_2$, and nicoteine, $C_{10}H_{12}N_2$, are also present in tobacco in lesser amounts.[152]

Myosmine, $C_9H_{12}N_2$, is an alkaloid[163] present in tobacco smoke. It has the same formula, less the methyl group on the nitrogen, as does nicotine. It is conveniently prepared by condensation of ethyl nicotinate with N-benzoylpyrrolidone followed by re-formation of a pyrrolidine ring.



[a] Condensation with the pyrrolidone by means of sodium ethoxide. [b] Hydrolysis of the cyclic amide and re-formation of a new ring, decarboxylation.

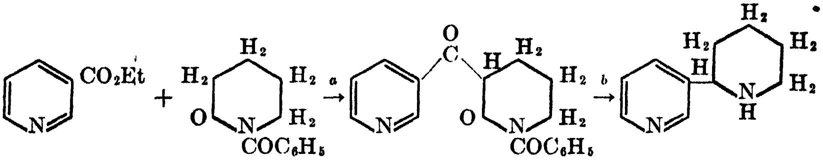
Anabasine is an isomer of nicotine. It was obtained by Smith as a by-product in the preparation of α,β-dipyridyl from pyridine and sodium (page 195) and was named neonicotine. Subsequently, Orechoff and Menshikoff[164] found that anabasine and neonicotine were identical save that the former was levoratatory rather than a *d,l* mixture. The structure is shown[165] by (*a*) dehydrogenation with silver acetate at 180° or with zinc dust to α,β-dipyridyl; (*b*) reduction with hydrogen and platinic oxide to an α,β′-dipiperidyl whose dinitroso derivative is identical with an authentic specimen; (*c*) oxidation with permanganate to nicotinic acid; (*d*) comparison with the other possible pyridylpiperidine, *viz.*, the 2,3′-isomer called also isoneonicotine, which by oxidation changes to α-picolinic acid. Anabasine is synthesized[166] from piperidone by a sequence of steps that parallels that for myosmine above. The dipicrate (m.p. 214°) and the dinitro-*m*-cresolate (m.p. 140 to 142°) of the synthetic compound are identical with those of the natural product.

---

[163] SPÄTH, WENUSCH, and ZAJIC, *Ber.*, **69**, 393 (1936).

[164] ORECHOFF and MENSHIKOFF, *ibid.*, **64**, 266 (1931).

[165] SMITH, *J. Am. Chem. Soc.*, **53**, 277 (1931).

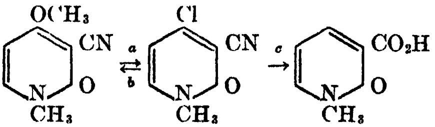


ᵃ NaOEt. ᵇ (1) HCl aq.; (2) $-CO_2$.

The anabasine content of *Anabasis aphylla, L.* (a plant that grows on the Russian steppes) is about 2 per cent. The alkaloid resembles nicotine, not only in its chemical structure but also in its toxicity to aphids and other soft-bodied insects. Of the six so far prepared, it is the only one of the nine possible piperidylpyridines that has any marked toxicity to insects.

Ricinine, $C_8H_8N_2O_2$, is a poisonous alkaloid contained in the seeds of *Ricinus communis*, the castor-oil plant. The plant has been cultivated since ancient times. The alkaloid was first isolated by Tuson,[167] who extracted the seeds with boiling water, filtered the solution, evaporated the filtrate to a thick sirup, and allowed it to crystallize.

Ricinine gives no color with ferric chloride. When refluxed with 5 per cent hydroxide, the alkaloid is converted to ricinic acid, $C_7H_6N_2O_2$, by loss of a methyl group. Phosphorus oxychloride converts ricinic acid to $C_7H_5ON_2Cl$, and this compound in turn is changed by hydrogen with palladium on barium carbonate to $C_7H_6ON_2$. When this last compound is refluxed with sodium in absolute alcohol, a carbamide, $C_7H_8O_2N_2$, is obtained by hydrolysis of a nitrile. Further alkaline hydrolysis gives a 1-methyl-2-pyridone carboxylic acid. The carboxyl group cannot be in the 4- or 5-position because those compounds are already known. The most likely structure is that pictured, and the following synthesis[168]—an excellent example of chemistry in this series—confirms this conjecture:



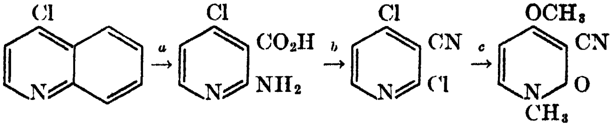
ᵃ Hydrolysis with KOH to ricinic acid, conversion to chloride by $POCl_3$. ᵇ Formation of ricinine by $NaOCH_3$. ᶜ Elimination of chloro group by hydrogenation over Pd on $BaCO_3$; hydrolysis of nitrile group.

---

[166] Späth and Mamoli, *Ber.*, **69**, 1082 (1936).

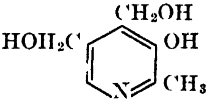
[167] Tuson, *J. Chem. Soc.*, **17**, 195 (1864).

[168] Späth and Koller, *Ber.*, **56**, 2454 (1923).



[a] Oxidation to the pyridine dicarboxylic acid by $KMnO_4$, formation of the anhydride by Ac_2O at 120°, conversion to the amide by NH_3, Hofmann degradation to the amine by Br_2 and alkali. [b] HNO_2 in H_2SO_4 to convert the amino group to hydroxyl, $POCl_4$ + PCl_5 to form the 2,4-dichloronicotinyl chloride, treatment with ammonia to form the amide, dehydration with $POCl_3$ to form the nitrile. [c] Treatment with sodium methoxide in boiling methanol to form the 2,4-dimethoxy compound, heat with methyl iodide in an evacuated tube at 120 to 130° to cause the change from O—CH_3 to N—CH_3.

Pyridoxine (vitamin B_6) is another member of the complex mixture originally designated as vitamin B. It is isolated from rice bran as the hydrochloride, $C_8H_{11}NO_3{\cdot}HCl$, (m.p. 204 to 206°). The free base melts at 160° and is optically inactive. The following facts permitted deduction of the structure.[169] It contains three active hydrogen atoms (Zerewitinov test), it has one methyl group, it gives a red color with ferric chloride which is comparable to that shown by β-hydroxypyridine, it has a basicity (6.2×10^{-10}) similar to that of β-hydroxypyridine (6.0×10^{-10}) and dissimilar to that of α-hydroxypyridine (1.7×10^{-13}); it has an absorption spectra that closely resembles those of 2-methyl-3-hydroxy-5-ethylpyridine, 2-methyl-5-hydroxypyridine, and β-hydroxypyridine; it yields a monomethyl ether with diazomethane which is oxidized by barium permanganate to a dicarboxylic acid, $C_9H_9O_5N$, (besides a lactone) which gives no color with aqueous ferrous sulfate (therefore not α) and forms a phthalein when fused with resorcinol (therefore vicinal). These facts indicate that the hydroxyl group is at C_3 and the two carboxyl groups are at C_4 and C_5. The location of the methyl group, relative to the hydroxyl, is determined by pyrolytic decarboxylation of the above sodium salt with lime, a process that simultaneously changes the methoxy to a hydroxy group. This hydroxymethylpyridine is not identical with the known 3-hydroxy-6-methylpyridine. Hence the methyl group is at C_2. Further confirmation of the position of the methyl group is given by the presence of a blue color fading to reddish brown when the vitamin is added to an alkaline suspension of 2,6-dichloroquinonechloroimide. Para-substituted phenols seldom give a blue color with this reagent.[170] Hence position 6 must be unoccupied.

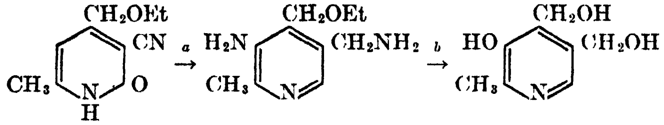


---

[169] STILLER, KERESZTESY, and STEVENS, *J. Am. Chem. Soc.*, **61**, 1237 (1939); KUHN and WENDT, *Ber.*, **72**, 305 (1939).

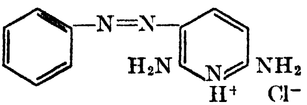
[170] GIBB, *J. Biol. Chem.*, **72**, 649 (1927); *cf.* THERIAULT, *Ind. Eng. Chem.*, **21**, 334 (1929).

The synthesis[171] of this vitamin, shown in the following steps, confirms the above skillful deduction of structure, and is an excellent example both of ring formation and of the special chemistry of the groups involved.

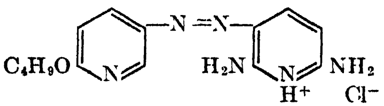


[a] The pyridine compound, which is the starting material in this sequence of reactions, is obtained from $CH_3C(O)CH_2C(O)CH_2OEtCO_2Et + H_2N(O)CCH_2CN$ with the aid of piperidine. From that point, HNO_3, PCl_5, H_2 over Pt to reduce the nitro compound and H_2 over Pt and Pd on charcoal to reduce the nitrile and eliminate the halogen atom are used. [b] HCl followed by HNO_2 in H_2SO_4 converts the two amino groups to hydroxy, HBr converts the ether to a bromide, and H_2O + AgCl causes hydrolysis of the bromide.

Pyridium is 2,6-diamino-3-phenylazo hydrochloride.



Pyridium



Neotropine

Compounds of this type are prepared by the action of diazonium salts on the active hydrogen atom in the 3-position of 2,6-diaminopyridine. The azo dye is an active antiseptic agent,[141] which led to its introduction as a urinary antiseptic. It apparently possesses little bactericidal power in vivo, however, and in recent years has been largely replaced by more effective agents such as methanamine, mandelic acid, and sulfanilamide. Neotropine is a similar dye made by coupling α-butyloxy-β'-aminopyridine with 2,6-diaminopyridine.

Sulfapyridine, i.e., 2-(*p*-aminobenzenesulfamido)-pyridine, 2-(*p*-$NH_2C_6H_4SO_2NH$)·C_5H_4N, is prepared[172] from acetylsulfanilyl chloride and 2-aminopyridine followed by removal of the acetyl group with hydrochloric acid. This compound is an important drug. It is one of the long line of pharmaceuticals[141] descended from Prontosil, *p*-$H_2NO_2SC_6H_4N{=}NC_6H_4SO_2NH_2$-*p*, the azo dye discovered by Klarer and Mietzsch in 1932 and found by Domagk in the same year to be active in streptococcal septicemia. Levaditi and Vaisman (1935) later found that the azo link was unnecessary. Since that time, a large number of pharmaceuticals of this type have been prepared and tested. The sulfanilamide drugs have proved a landmark in the treatment of diseases of bacterial origin. The Nobel prize was offered to Domagk in 1939 for his discovery.

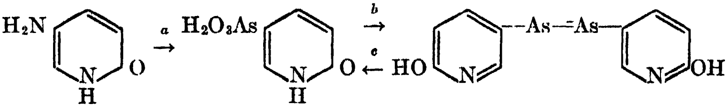
Pyridine Mercurials.—The reaction of pyridine with mercury acetate at 155° for 2½ hr. in the presence of 1 mole equivalent of water yields 3-pyridylmercuric acetate (m.p. 178°), convertible to the chloride or nitrate by reaction with sodium chloride or nitrate, respectively. α-Aminopyridine and α-picoline are mercurated in the 5-position at 100 and 150°, respectively. The compounds are stable to 20 per cent sodium hydroxide. Pyridine mercuric compounds[173] are not precipitated by proteins and have a strong germicidal action with relatively low host toxicity. Amino and methyl groups lower the germicidal activity.

---

[171] HARRIS and FOLKERS, *J. Am. Chem. Soc.*, **61**, 1245 (1939).

[172] WINTERBOTTOM, *ibid.*, **62**, 160 (1940).

Pyridine Arsenicals.—The toxic properties of pyridine compounds are greatly reduced by using derivatives of pyridone.[174] When the substituent is an arsonic acid or an arseno system, the compound has a valuable trypanocidal action. 2-Pyridone-5-arsonic acid and 2,2′-dihydroxy-5,5′-arsenopyridine and 3,3′-diamino-2,2′-dihydroxy-5,5′-arsenopyridine all have properties similar to those of salvarsan. Preparation of the arsonic acid is effected from 5-amino-2-pyridone (itself made from α-aminopyridine by nitration, hydrolysis, and reduction) by the customary diazotization and treatment with arsenious oxide. This compound is then converted by sodium hypophosphate with a little potassium iodide into the arseno derivative.[175]



[a] $HNO_2 + HX, As_2O_3$. [b] $NaH_2PO_2 + KI$. [c] H_2O_2.

These compounds in turn can be converted to the N-substituted pyridones by the conventional reaction with an alkyl iodide or with chloroacetic acid. Some of these compounds have valuable therapeutic properties.[174]

The 3,3′-diaminoarseno compound[176] is prepared by nitration of the above arsonic acid, followed by reduction with hypophosphite. Reduction of the arsonic acid derivative with zinc dust and sulfuric acid yields the corresponding arsine[174] ($RAsH_2$ where R = the pyridone system). Mild reduction of the acid with sulfur dioxide in the presence of potassium iodide and sulfuric acid yields the arsine oxide RAsO. 2-Pyridone-3-arsonic acid may also be prepared, since nitration of α-aminopyridine yields a 3-nitro as well as a 5-nitro product that can be subjected to the customary sequence of reactions. The toxicity of compounds in the 3-series is, however, generally higher than that of compounds with substituents in the 5-position.[174]

---

[173] Swaney, Skeeters, and Shreve, *Ind. Eng. Chem.*, **32**, 360 (1940).

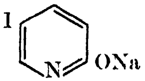
[174] Binz and Räth, *Ann.*, **453**, 238 (1927); **455**, 127 (1927); Binz, *Z. angew. Chem.*, **48**, 425 (1935); Binz, Maier-Bode, and Rost, *ibid.*, **44**, 835 (1931); Binz, *Ber.*, **70A**, 127 (1937).

[175] Binz and Räth, *Ann.*, **455**, 127 (1927).

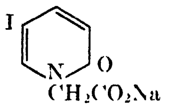
[176] Binz, Räth, and Urbschat, *ibid.*, **475**, 136 (1929).

Iodopyridone Compounds.—Iodopyridones[177] are valuable agents for producing X-ray contrast effects for visualization of the urinary tract. They have a low toxicity, a high percentage of iodine, and a reasonably high transmission of light at the wave length employed in radiography. These compounds are an outgrowth of the work of Binz and Räth, who observed that, as a class, the pyridones were less toxic than the pyridines. Synthesis of uroselectan, sometimes called Iopax, is accomplished by conventional steps from α-aminopyridine in which the 5-iodo group can be introduced by iodination, the amino group is replaced by a hydroxy group by diazotization and hydrolysis, and the acetic acid is introduced by means of chloroacetic acid and alkali. Uroselectan B is obtained from cheledamic acid by direct iodination, followed by formation of the N-methyl derivative.

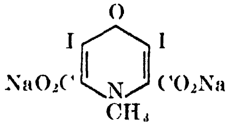
Diodrast is obtained from γ-pyridone by means of iodine followed by chloroacetic acid. The formulas are shown below.



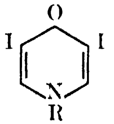
Selectan
52% I_2



Uroselectan
or Iopax
42% I_2



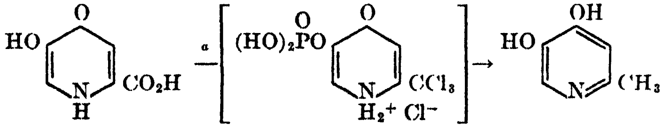
Uroselectan B
51.9% I_2



Diodrast
or Perabrodil
49.8% I_2

R = $-CH_2CO_2H{\cdot}NH(CH_2CH_2OH)_2$.

Comenamic acid is obtained from comenic acid (page 155) and ammonia at 100°. This compound undergoes a remarkable transformation[178] when the product of its reaction with 3 moles (4.4 parts by weight) of phosphorus pentachloride at 150° is poured with vigorous stirring into ice water, the amorphous precipitate is digested at room temperature with tin and 10 per cent hydrochloric acid for a long time until dissolved, and the mixture is heated on a water bath for some hours. The final product is 4,5-dihydroxy-2-methylpyridine. The intermediate product of this reaction may be a compound with phosphoric acid, which is responsible for this peculiar conversion of a carboxyl to a methyl group. This reaction has already been mentioned in connection with the proof of the constitution of kojic acid.



[a] PCl_5 at 150°, H_2O, Sn + 10 per cent HCl.

---

[177] BINZ, RÄTH, and LICHTENBERG, *Z. angew. Chem.*, **43**, 452 (1930); BINZ, *Ber.*, **70A**, 127 (1937).

[178] OST, *J. prakt. Chem.*, **27**, 257 (1883); BELLMAN, *ibid.*, **29**, 14 (1884); YABULA, *J. Chem. Soc.*, 575 (1924); VERKADE, *Rec. trav. chim.*, **43**, 879 (1924).

Problems

1. Name the product obtained from each of the following reactions: (*a*) Isobutyraldehyde with 2 mole equivalents of ethyl acetoacetate in alcoholic ammonia.[9] (*b*) Acetone, butyraldehyde, and ammonia over alumina or kaolin at 305 to 310°.[8] (*c*) The hydrochloride of the *p*-dichlorodianilide of glutaconic aldehyde heated in a vacuum at 80°.[72] (*d*) An alcoholic solution of benzoylacetone and cyanoacetamide treated with diethyl amine.[179] (*e*) A mixture of ethyl benzoylacetate and benzaldehyde treated with a few drops of diethylamine and, after some time, the product heated with a concentrated aqueous solution of hydroxyl amine for 4 hr. at 120 to 130°.[11] (*f*) Paraldehyde, concentrated ammonium hydroxide, and ammonium acetate heated at 180° for 8 hr.[180] (*g*) Benzoylacetaldehyde and ethyl aminocrotonate (how prepared?) in ether.[181] (*h*) Ethyl formate condensed with phenyl ethyl ketone by means of sodium ethoxide and the product of this reaction heated with ethyl β-aminocrotonate on a water bath for 15 hr.[182] (*i*) Paraldehyde and acetamide heated in a tube at 280° so as to form $C_8H_{11}N$.[106b]

2. Name the product that results from the following transformations of pyridine compounds: (*a*) Sodium pyridine-β-sulfonate heated with potassium cyanide in a retort.[38] (*b*) Sym-collidine heated for 3 hr. on a water bath with absolute nitric acid and fuming sulfuric acid.[183] (*c*) 2,3,5-Trichloropyridine heated in a sealed tube with aqueous ammonia.[116,117] (*d*) 2-Chloro-5-nitropyridine with sodium sulfide and the product of this reaction treated with stannous chloride.[184] (*e*) Same as (*d*) but the product of the first step treated with potassium dichromate.[184] (*f*) 4-Pyridone treated with phosphorus pentasulfide and the product allowed to react with hydrogen peroxide.[144] (*g*) 2-Aminopyridine heated at 230 to 250° for 30 hr. with 2-aminopyridine hydrochloride.[185] (*h*) 2-Bromopyridine (how prepared?) heated with 2-aminopyridine in the presence of potassium carbonate and copper bronze with a trace of potassium iodide in boiling mesitylene for 16 hr.[185] (*i*) Nicotine heated in boiling toluene with sodamide.[44b] (*j*) 4,6-Dichloro-2-aminopyridine dissolved in concentrated hydrochloric acid and treated with sodium nitrite.[186] (*k*) 2-Bromopyridine heated with 2-anilinopyridine in mesitylene with copper bronze.[120] (*l*) 2-Hydroxy-3,5-dichloropyridine in alcoholic potash with methyl iodide and the product heated with phosgene in toluene for 3 hr. at 150°.[113] (*m*) Pyridine allowed to stand for 3 hr. with an equivalent quantity of isobutyl iodide and the product of this reaction treated with potassium ferricyanide in the presence of caustic soda.[187] (*n*) Phenyllithium with pyridine in ether solution followed by replacement of the ether with toluene and the application of heat.[188] (*o*) Bromine and 5-nitro-2-aminopyridine.[189] (*p*) A mixture of cetyl chloride, α (or γ)-picoline, and sodamide, allowed to stand for 2 days.[103b] (*q*) α-Pyridinemercaptan dissolved in an equivalent amount of alkali and treated with iodine.[143]

[179] Bardhan, *J. Chem. Soc.*, 2223 (1929).

[180] Langer and Haumeder, *J. prakt. Chem.* [2], **150**, 153 (1938).

[181] Späth and Burger, *Monatsh.*, **49**, 265 (1928).

[182] Baser, *J. Indian Chem. Soc.*, **12**, 289 (1935).

[183] Van Rijn, *Rec. trav. chim.*, **45**, 267 (1926); Plazek, *Ber.* **72**, 577 (1939).

[184] Surrey and Lindwall, *J. Am. Chem. Soc.*, **62**, 173 (1940).

[185] Wibaut and LaBastide, *Rec. trav. chim.*, **52**, 493 (1933).

[186] Graf, *J. prakt. Chem.* [2], **133**, 36 (1932).

[187] Decker and Kaufmann, *J. prakt. Chem.* [2], **84**, 425 (1911).

[188] Walters and McElvain, *J. Am. Chem. Soc.*, **55**, 4625 (1933).

[189] Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 492 (1920); *C.A.*, **18**, 1495 (1924).

3. Devise methods for the preparation of the following compounds from pyridine as one of the reagents. (*a*) α-(4-Methoxyphenyl)-pyridine.[4d] (*b*) 2-Amino 5-pyridinesulfonic acid.[7c] (*c*) 2,6-Diamino-4-bromopyridine.[122] (*d*) 5,5′-Dinitro-2,2′-dipyridine disulfide, $C_{10}H_6N_2O_4S_2$.[145] (*e*) 2-Chloro-5-nitropyridine.[190] (*f*) 2-Isoamyloxypyridine-5-arsonic acid.[191] (*g*) 2-(*o*-nitrophenyl)-pyridine by a method that leaves no doubt as to the structure.[43] (*h*) 2-Butoxypyridyl-5-azo-3′,5′-diaminopyridine.[192] (*i*) 2-Chloro-5-bromopyridine.[193] (*j*) 2-Aminopyridine-4-sulfonamide, the pyridine analogue of sulfanilamide, by two methods.[194] (*k*) β (4-pyridyl)-acrylic acid.[98b] (*l*) 3-Pyridylchloroarsine hydrochloride.[111]

4. Nitration of 4-phenylpyridine yields a mixture of three nitro products. Devise a method for the determination of the position of the nitro group.[43,75]

5. Name the product that results from the following sequence of reactions: (*a*) Ethyl cyanoacetate treated with sodium in absolute alcohol, and, as soon as the sodium has dissolved, treated with ethyl oxaloacetate (itself prepared from ethyl acetate and ethyl oxalate under the influence of sodium alkoxide), and the mixture then refluxed for 1 hr. (*b*) The product from the first step allowed to stand with cold concentrated sulfuric acid for 12 hr.[195]

6. From 44 runs, each with 6.5 g. of propionaldehyde and 4 g. of propionaldehyde ammonia at 205 to 210° for 6 hr., a mixture of dry crude bases, which amounted to 40 per cent of the theoretical yield, was obtained. Piperidines were first separated by use of potassium nitrite. After 20 fractionations (the modern efficient fractionating columns were not then known), the mixture of pyridine bases was separated into two parts which boiled at 197 to 199° and 219 to 221°. The first fraction was further purified as the double salt of mercuric chloride. By careful oxidation of this purified base (*A*) with potassium permanganate and decarboxylation of the product a base was obtained which had the composition C_7H_9N. This base on further oxidation with the same reagent yielded pyridine-3,5-dicarboxylic acid. What possibilities in structure existed for the original base (*A*)?[5k]

7. What is the final product that results from the following sequence of reactions in which the product from each step is treated in turn with the reagent designated in the next step? (*a*) Ethoxyacetylacetone (how prepared?) and piperidine added with shaking to cyanoacetamide dissolved in hot alcohol. (*b*) Crystals from (*a*) heated with concentrated hydrochloric acid at 120 to 125° for 4 hr. (*c*) Fuming nitric acid and concentrated sulfuric acid at 35 to 45°. (*d*) Phosphorus oxychloride and phosphorus pentachloride. (*e*) Hydrogen and platinum oxide catalyst at 3 atm. pressure until 3 moles of hydrogen are absorbed. (*f*) Hydrogen and platinum oxide, hydrogen with palladium on barium carbonate. (*g*) Sodium nitrite and sulfuric acid and the diazo solution then added to 50 per cent sulfuric acid. (*h*) Diazomethane in dry ether. (*i*) Barium permanganate. The composition after (*d*) is $C_8H_5N_2O_4Cl$, after (*f*) is $C_8H_8N_2O_2$, and at the end is $C_9H_9O_5N$.[196]

8. Write the equations for changes that begin with α-pyrrolidone (itself obtained by electrolytic reduction of succinimide at a lead cathode in acid solution), employ the following reagents in sequence, and end with a compound that has the formula

---

[190] Räth, *Ann.*, **486**, 71 (1931).

[191] Binz, Maier-Bode, and Morisawa, *Z. angew. Chem.*, **46**, 349 (1933).

[192] Binz and von Schickh, U.S.P. 2,145,579; *C.A.*, **33**, 3599 (1939).

[193] Chichibabin and Builinken, *J. Russ. Phys. Chem. Soc.*, **50**, 471 (1920); *C.A.* **18**, 1494 (1924).

[194] Naegeli, Kundig, and Brandenberger, *Helv. Chim. Acta*, **21**, 1746 (1938).

[195] Rogerson and Thorpe, *J. Chem. Soc.*, **89**, 631 (1906).

[196] Harris, Stiller, and Folkers, *J. Am. Chem. Soc.*, **61**, 1242 (1939).

$C_{10}H_{14}N_2$. (*a*) α-Pyrrolidone sodium in dry benzene treated dropwise with dimethylsulfate. (*b*) Ethyl nicotinate and sodium ethoxide. (*c*) One hundred cubic centimeters of fuming hydrochloric acid for 7 hr. at 130° in a bomb tube (ketone splitting) to give a compound with the formula $C_{10}H_{14}N_2O$. (*d*) Zinc dust and alcoholic alkali. (*e*) Concentrated hydriodic acid and red phosphorus at 100° in a bomb tube for 6 hr. (*f*) Aqueous caustic potash to give the product $C_{10}H_{14}N_2$.[197]

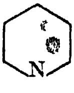
9. What are the equations for the changes that begin with pyridine, use each of the following reagents in sequence, and end with the compound $C_9H_{12}N_2$? (*a*) Pyridine (400 g.) 100 cc. of water and 30 g. of vanadyl sulfate with 600 cc. of concentrated sulfuric acid heated over a free flame until sulfuric acid begins to distill; the mixture, cooled, treated with 800 cc. of 20 per cent fuming acid, again heated gently for 2 hr., and, finally at the full force of a bunsen burner, until most of the acid has distilled and the contents weigh approximately 900 g. (*b*) Mixed with sodium cyanide and heated in a retort. (*c*) Ethoxypropylmagnesium bromide (how prepared?) and the Grignard product hydrolyzed as usual with water and acid to give a compound with the composition $C_{11}H_{15}O_2N$. (*d*) Hydroxylamine hydrochloride followed by zinc dust and acetic acid. (*e*) Forty-eight per cent hydrobromic acid at 150 to 155° for 12 hr., after which the excess acid is removed by distillation at reduced pressure, and the viscous product treated with aqueous potassium hydroxide in order to recover the crude compound which, after purification, has the composition $C_9H_{12}N_2$.[198]

10. What is the product of the following succession of changes? (*a*) 2,6-Dibromopyridine ($\frac{1}{10}$ mole) refluxed for 2 hr. on a water bath with $\frac{1}{5}$ mole of dimethyl sulfate. (*b*) The aqueous solution from the above step treated with $\frac{1}{10}$ mole of 10 per cent caustic soda. (*c*) The product from (*b*) heated with a mixture of phosphorus penta- and tri-bromide in a sealed tube at 190° for 6 hr.[199]

11. Chlorosulfonic acid or sulfur trioxide with pyridine in carbon tetrachloride forms $C_5H_5NSO_3$. This compound decomposes with hot water into pyridine and sulfuric acid. Cold 20 per cent sodium hydroxide after a short term produces about 80 per cent of the sodium salt of a hydroxybutadiene aldehyde, $C_5H_6O_2$, identified by means of the benzoyl derivative. What are the changes that probably have occurred?[200]

12. Show a method for proving the structure of the product that results from the reaction of ethyl propionylpyruvate, cyanoacetamide, and piperidine.[201]

13. Suggest a method for obtaining the inaccessible γ-picoline from the easily procurable 2,4-dimethylpyridine.[202]



14. When devising methods for synthesis of pyridine compounds, divide the framework into likely divisions, as indicated by the example, consider that a carboxyl group is equivalent to a hydrogen atom—since decarboxylation can always be applied—and keep in mind, particularly, such starting reagents as ethyl acetoacetate, ethyl oxaloacetate, ethyl cyanoacetate, β-aminocrotonate, etc. The presence of like groups symmetrically placed on either side of the pyridine nucleus often furnishes a clue to the type of synthesis. Devise methods for synthesizing the following pyridine compounds from noncyclic reagents: (*a*) Ethyl 2,6-dihydroxypyridine-4,5-dicarboxylate.[195] (*b*) 2-Methyl-6-tertiary butylpyridine-3,4-dicarboxylic acid (how prove the position of the carboxyl group?).[16] (*c*) 2,4,6-Triphenylpyridine N-oxide.[63] (*d*) 4,5-Dimethyl-2,6-dihydroxypyridine.[14] (*e*) 3-Cyano-4-carbethoxy-6-methyl-2-pyridone.[179] (*f*) 2-Methyl-3 (β-ethoxyethyl)-4,6-dihydroxy-5-carbethoxypyridine.[203] (*g*) Ethyl 2,6-dimethylpyridine-3-carboxylate.[204] (*h*) 2,4-Di-*p*-tolyl-3-cyano-6-aminopyridine.[205] (*i*) Citrazinic acid which is 2,6-dihydroxypyridine-4-carboxylic acid.[195] (*j*) 2,6-Dimethyl-4-ethyl-3,5-dicarbethoxypyridine.[206]

---

[197] Späth and Bretschneider, *Ber.*, **61**, 327 (1928).

[198] Craig, *J. Am. Chem. Soc.*, **55**, 2854 (1933).

[199] Wibaut, Speckman, and Van Wagtendonk, *Rec. trav. chim.*, **58**, 1100 (1939).

[200] Baumgarten, *Ber.*, **57**, 1622 (1924); **59**, 1166 (1926); **65**, 1637 (1932).

[201] Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941).

[202] Clemo and Gourlay, *J. Chem. Soc.*, 478 (1938).

15. α-Pyridone has been synthesized from malic acid. Show a sequence of steps by which this preparation can be effected.[131a]

16. The 2-methyl homologue of coramine has no analeptic action but actually damages the heart muscle of a frog. Devise a method for the preparation of this compound from malonic dialdehyde as one of the reagents. In practice, the malonic dialdehyde is unstable, but the ether acetal of the enol form, $(EtO)_2CHCH{=}CHOEt$, can be employed.[207]

17. Suggest a method for the preparation of 2,6-dihydroxy-4-methylpyridine, and then name the product derived from this compound by use of the following reagents in sequence: (*a*) Malic acid with concentrated sulfuric acid on a steam bath for 5 to 6 hr. to give $C_9H_7O_3N$. (*b*) Bromine added in small portions to an acetic acid solution of the product from (*a*). (*c*) The $C_9H_5O_3NBr_2$ product boiled with ethyl alcoholic potash to yield $C_9H_6O_4NBr$. (*d*) Refluxed with 10 per cent aqueous sodium hydroxide and zinc dust to give $C_9H_7O_4N$. (*e*) Treated with a boiling solution of acetic and concentrated sulfuric acid in order to form $C_8H_7O_2N$. (*f*) Heated with phosphoryl chloride in a sealed tube at 170 to 180°. (*g*) Refluxed with 95 per cent hydrazine hydrate for 4 hr. to yield $C_8H_9ON_3$. (*h*) Gently heated with copper sulfate in acetic acid to give an oil, the picrate of which has the composition $C_8H_7ON \cdot C_6H_3O_7N_3$.[208]

18. Ethyl ethylacetoacetate is condensed with ethyl cyanoacetate to form two different products depending on whether (*a*) ammonia or (*b*) sodium and then sodium hydroxide is used as the agent. What is the product formed in each case? How proceed from these compounds to the preparation of β-collidine?[209]

19. Trigonelline, $C_7H_7O_2N$, is an alkaloid that occurs in the foenugree seeds from the leguminous plant *Trigonella foenumgraecum* which is found in India and Egypt. The seeds are used in preparation of curries and as a veterinary spice. The alkaloid is also found in garden peas, hemp, and elsewhere. It is prepared in the laboratory by treating nicotine methiodide with silver oxide. What is the structure of the compound? To what class of substance does it belong?[210] What properties would it exhibit?

20. Devise a procedure for the preparation of β-vinylpyridine from a pyridine compound.[211]

[203] Tracy and Elderfield, *J. Org. Chem.*, **6**, 54 (1941).

[204] Rabe, *Ber.*, **45**, 2163 (1912).

[205] Meyer, Berger, Oehler, and Schletter, *J. prakt. Chem.* [2], **90**, 29 (1914).

[206] Siddiqui, *J. Indian Chem. Soc.*, **16**, 410 (1939).

[207] Baumgarten and Dornow, *Ber.*, **72**, 563 (1939).

[208] Robinson and Watt, *J. Chem. Soc.*, 1536 (1934).

[209] Ruzicka and Fornasir, *Helv. Chim. Acta*, **2**, 338 (1919).

[210] Hantzsch, *Ber.*, **19**, 31 (1886); Johns, *ibid.*, **20**, 2840 (1887).

[211] Iddles, Lang, and Gregg, *J. Am. Chem. Soc.*, **59**, 1945 (1937).

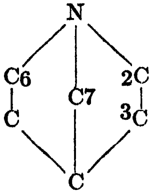
CHAPTER IX

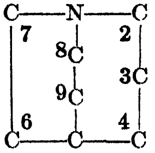
PIPERIDINE AND RELATED COMPOUNDS

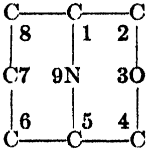
Many natural products, chiefly alkaloids, contain a reduced pyridine ring, often as part of a bicyclic system. The methods for the preparation of such compounds are frequently applicable also to other heterocyclic rings and to five-membered rings. The discussion in this chapter is, therefore, general, though concerned primarily with compounds that have a piperidine ring.

Naming and Numbering.—Monocyclic piperidine compounds are numbered in the same way as are the pyridines. If a substituent is attached to nitrogen, the compound may be referred to as a piperidino derivative, *e.g.*, γ-piperidinopropyl benzoate is $\overline{C_5H_{11}N}$—$CH_2CH_2CH_2O_2CC_6H_5$; if attached to carbon, it is called a piperidyl product.

Bicyclic systems are named as if they were carbocyclic compounds with nitrogen or other hetero atom replacing carbon. Numbering begins at one of the bridge ends, the heterocyclic end, if one is present.[1] If more than one hetero atom is present, precedence is given to that one which is in the highest group in the periodic table and has the lowest atomic number in that group. On this basis, the order will be O, S, Se, Te, N, P, As, Sb, Si, Sn, Pb, and Hg. From the 1-position, numbering progresses in the order of the longest path to the other end of the bridge, then back to the 1-position by the next longest path, and finally across the bridge, which is often placed in the center of the structural formula. When the compound is named, the number of atoms in each path is arranged in descending order and placed in brackets. These principles are illustrated by the three formulas pictured below for 1-azabicyclo[2.2.1]-heptane, 1-azabicyclo[3.2.2]nonane, and 3-ox-9-azabicyclo[3.3.1]nonane, respectively.





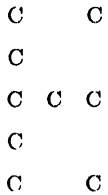


---

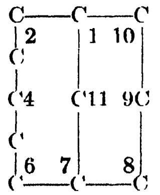
[1] Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, 1940.

When writing the structural formulas from such names, it is a good plan first to write the three divisions indicated in the brackets as if all the atoms were carbon, with the smallest number in the center; then insert two carbon atoms for the bridge ends and number the atoms; and, finally, replace the carbon with the hetero atoms. For example, 3,5-dithiabicyclo[5.3.1]henadecane would be constructed as in stage (*A*) with the 5.3.1 atoms in the appropriate order; then as in stage (*B*) with the bridge ends in place and the numbering completed; and finally, in stage (*C*) with the two sulfur atoms in place of the carbon at positions 3 and 5 and the hydrogen, or other substituents, attached.

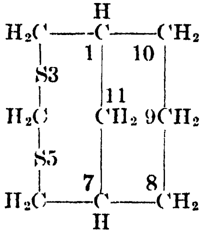
A



B

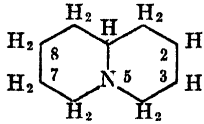


C

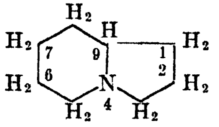


Numbering systems derived from well-known heterocyclic types and empirical names are sometimes encountered. For example, octahydroquinolizine [see (*A*) below] is considered as a derivative of quinolizine in which numbering starts in the alpha position of one of the rings so that

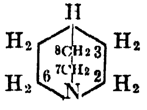
A



B



C

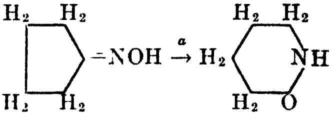


nitrogen will be accorded the smallest number possible. So also is octahydroindolizine (pyrrocoline) (*B*) regarded as a derivative of indolizine. The numbering begins as in indole with the smaller sized ring. On the other hand, quinuclidine (*C*) has no well-known parent conjugated or aromatic system from which it is derived. Hence its numbering is made in accordance with the name 1-azabicyclo[2.2.2]octane. Some compounds have several empirical names. Octahydroquinolizine, for example, is known also as octahydropyridocoline, piperidocoline, and norlupinane. Alternatives for octahydroindolizine are octahydropyrrocoline, octahydropyrindole, piperolidine, and coniceine.

Synthesis of Piperidine Compounds.—Piperidines and their derivatives can be made by (*a*) reduction of pyridine compounds, (*b*) expansion of a five- to a six-membered ring, and (*c*) use of appropriate links that unite the ends of a chain or the segments of a chain. The agents for reduction are conventional ones employed in many organic processes. For example, sodium[2] in boiling absolute alcohol or tin[3] with hydrochloric acid is used repeatedly. The former agent produces also some tetrahydropiperidine,[4] especially when there is an ethyl group at C_3.

Reduction may also be accomplished electrolytically in 20 per cent sulfuric acid at a lead cathode.[5] Catalytic hydrogen over platinum[6] or Raney nickel[7] may be employed. Hydrogen at 200 to 400 atm. and 250 to 260°C. over copper–chromium oxide catalyst[8] reduces glutarimides and glutaramides to piperidine compounds. This last process converts also the homologous five- and seven-ring systems to pyrrolidines and azepines, respectively.

Ring enlargement takes place very readily by means of a variation of the Beckmann rearrangement whereby the oxime of a cyclopentanone becomes a piperidone.



[a] Warmed with 100 parts of conc. H_2SO_4 to 20 parts of water.

The reaction[9] is general. A cyclohexanone oxime becomes a seven-membered ring; a cycloheptanone changes to a ring of eight atoms.

Formation of rings by closing a chain or uniting fragments is a very common practice. Four examples where this union occurs at the nitrogen atom are given below.

$$\text{I.}\quad XCH_2(CH_2)_3CH_2X \xrightarrow{a} CH_2(CH_2CH_2)_2NH$$

$$\text{II.}\quad XCH_2(CH_2)_3CH_2NHR \xrightarrow{b} CH_2(CH_2CH_2)_2NR$$

$$\text{III.}\quad XH_3NCH_2(CH_2)_3CH_2NH_3X \xrightarrow{c} CH_2(CH_2CH_2)_2NH$$

$$\text{IV.}\quad C_6H_5C(O)(CH_2)_3CH_2Br \xrightarrow{d} C_6H_5\overline{CH(CH_2)_4N}H$$

[a] Reflux with NH_3 in ether.[10] [b] NaOH or NH_3.[11] [c] Heat.[12] [d] The corresponding phthalimide is heated with CH_3CO_2H and fuming HCl at 138° after which the tetrahydro product is reduced to the piperidine.[13]

---

[2] LADENBURG, *Ber.*, **17**, 156, 388 (1884).

[3] KOENIGS, *ibid.*, **14**, 1852 (1881).

[4] CHICHIBABIN, *ibid.*, **38**, 3834 (1905); KOENIGS, *ibid.*, **40**, 3199 (1907).

[5] EMMERT and DORN, *ibid.*, **48**, 687 (1915); EMMERT, *ibid.*, **46**, 1716 (1913).

[6] SKITA and MEYER, *ibid.*, **45**, 3589 (1912).

[7] ADKINS, KERICK, FARLOW, and WOJCIK, *J. Am. Chem. Soc.*, **56**, 2425 (1934).

[8] PADEN and ADKINS, *ibid.*, **58**, 2487 (1936).

[9] WALLACH, *Ann.*. **312**. 171 (1900); BECKMANN and MEHRLÄNDER, *ibid.*, **289**, 362 (1896).

[10] v. BRAUN, *Ber.*, **41**, 2156 (1908).

[11] GABRIEL, *ibid.*, **25**, 415 (1892).

[12] LADENBURG, *ibid.*, **18**, 3100 (1885); *Ann.*, **247**, 1 (1888).

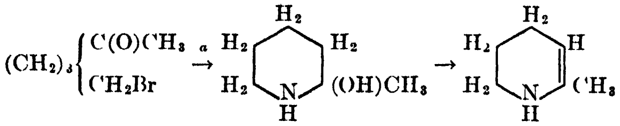
[13] GABRIEL, *Ber.*, **41**, 2010 (1909).

So smooth is the formation of piperidines from dibromopentane and primary amines (I) that the reaction can be used as a diagnostic process[9] for primary, secondary, and tertiary amines. Primary amines (except *o*-substituted anilines that produce diamino derivatives) yield piperidine derivatives that can be distilled. Secondary amines form quaternary piperidinium salts according to the equation

$$Br(CH_2)_5Br + 2HNR_2 \rightarrow CH_2(CH_2CH_2)_2NR_2^+ + R_2NH_2^+ + 2Br^-$$

Tertiary amines form the diammonium bromide.

Ring closure of the type shown in IV produces tetrahydro compounds from δ-bromoketones.[14] Such reagents probably form a δ-amino ketone as the first phase, the chain then undergoes an internal condensation of the aldol type, and water splits from the hydroxypiperidine as illustrated below.



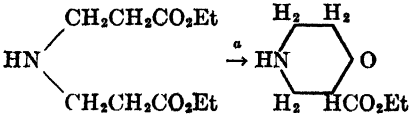
[a] Aqueous or alcoholic ammonia   Ring closure occurs without heat.

All tetrahydro pyridines are, of course, readily reducible to piperidines by one of the methods previously mentioned.

A major problem in using these synthetical methods is to obtain the appropriate intermediate. Methods for expanding the carbon chain from the readily available ethylene bromide, trimethylene bromide, chlorobromopropane (from allyl chloride and hydrobromic acid) or other reagents are listed in Table I.

A modification of one of these methods consists of opening any tetrahydropyrane ring by means of strong hydrobromic acid and then re-forming the closed system by means of alcoholic ammonia. Many examples of this practice as applied to bicyclic compounds will be given a little later in this chapter.

The ends of a chain can be joined at other positions than at the nitrogen. For example, a carbon-carbon union is realized by the Dieckmann reaction—treatment of an appropriate diester with sodium in boiling toluene or xylene.[15] The necessary diester is prepared from



[a] Na in hot toluene or xylene.

---

[14] Lipp, *ibid.*, **25**, 2190 (1892).

[15] (*a*) Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920); (*b*) Kuettel and McElvain, *J. Am. Chem. Soc.*, **53**, 2692 (1931).

TABLE I.—SEQUENCE OF STEPS FOR EXPANDING THE CHAIN IN ORDER TO PREPARE INTERMEDIATES FOR RING CLOSURE

Starting material	Reagent for obtaining each product from the previous compound	Sequence of products arranged to show expansion of original methylene groups
$Cl(CH_2)_3Br$[16]	(1) KCN	$Cl—(CH_2)_3—CN$
	(2) $NaOC_6H_5$ in abs. alc.	$C_6H_5O—(CH_2)_3—CN$
	(3) Na + abs. alc.*	$C_6H_5O—(CH_2)_3—CH_2NH_2$
	(4a) HCl at 180–185°*	$Cl—(CH_2)_3—CH_2NH_2$
	or	
	(4b) $(C_6H_5CO)_2O$ at 180°	$C_6H_5O—(CH_2)_3—CH_2N{=}C_8H_4O_2$
	(5b) saturated with HBr at 0°, heated 100°	$Br—(CH_2)_3—CH_2N{=}C_8H_4O_2$
	(6b) $NaCH(COOEt)_2$	$(COOEt)_2CH—(CH_2)_3—CH_2N{=}C_8H_4O_2$
	(7b) 1.49 sp. gr. HBr. Reflux	$COOH\ CH_2—(CH_2)_3—CH_2NH_2$
$C_6H_5O(CH_2)_4NH_2$[17] from (3) above	(1) $(C_6H_4CO_2)O$ at 180°	$C_6H_5O—(CH_2)_4—N{=}C_8H_4O_2$
	(2) Sat'd. with gaseous HBr. 0°. Heated to 100°.	$Br—(CH_2)_4—N{=}C_8H_4O_2$
	(3) $CH_3C(O)CH(Na)COOEt$	$\left.\begin{matrix}CH_3C(O)\\EtO_2C\end{matrix}\right\}CH(CH_2)_4—N{=}C_8H_4O_2$
	(4) 20% KCl. Carbethoxy splitting	$CH_3COCH_2—(CH_2)_4—N{=}C_8H_4O_2$
	(5) Fuming HCl in CH_3COOH at 168°	$CH_3COCH_2—(CH_2)_4—NH_2$

---

* Order of use of these two reagents may be reversed.

[16] GABRIEL and COLMAN, *ibid.*, **41**, 2014 (1908); GABRIEL, *ibid.*, **24**, 3231 (1891); **42**, 1249 (1909).

[17] GABRIEL, *ibid.*, **42**, 1249 (1909).

TABLE I.—SEQUENCE OF STEPS FOR EXPANDING THE CHAIN IN ORDER TO PREPARE INTERMEDIATES FOR RING CLOSURE.—(*Continued*)

Starting material	Reagent for obtaining each product from the previous compound	Sequence of products arranged to show expansion of original methylene groups
$Cl(CH_2)_3Br$[11]	(1) $NaOC_6H_5$ in abs. alc.	$Cl—(CH_2)_3—OC_6H_5$
	(2) $NaCH(COOEt)_2$	$(COOEt)_2CH—(CH_2)_3—OC_6H_5$
	(3) 33 % KOH in abs. alc., HX, heat	$(COOH)CH_2—(CH_2)_3—OC_6H_5$
	(4) Heated with $Pb(SCN)_2$	$CNCH_2—(CH_2)_3—OC_6H_5$
	(5) Na + alc.	$NH_2CH_2CH_2—(CH_2)_3—OC_6H_5$
	(6) Conc. HCl. 3 hr. 180°	$NH_2CH_2CH_2—(CH_2)_3—Cl$
H_2CO[18]	(1) Two equivalents of $H_2C(COOEt)_2$	$(EtOOC)_2HC—(CH_2)$ $—CH(COOEt)_2$
	(2) Conc. H_2SO_4 at 100°	$(HOOC)CH_2—(CH_2)$ $—CH_2COOH$
	(3) H_2 at 200–300 atm. Copper-chromium oxide	$HOCH_2CH_2—(CH_2)$ $—CH_2CH_2OH$
$Br(CH_2)_3Br$[19]	(1) KCN in alc.	$NC—(CH_2)_3—CN$
	(2) Na and EtOH	$H_2HCH_2—(CH_2)_3—CH_2NH_2$
$H_2C(COOEt)_2$[20]	(1) 5-Ethoxypentanol-1* with HBr, $NaCH(CO_2Et)_2$	$EtO(CH_2)_5—CH$ $—(COOEt)_2$
	(2) $Br(CH_2)_5OEt$ + Na	$EtO(CH_2)_5—C[(CH_2)_5OEt](CO_2Et)_2$
	(3) KOH, HX, heat	$EtO(CH_2)_5—CH[(CH_2)_5OEt]CO_2H$

---

* From ethoxy *n*-valerianic acid or from pentamethylene glycol.

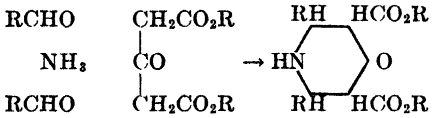
[18] ADKINS, FOLKERS, and WOJCIK, *J. Am. Chem. Soc*, **54**, 1145, 4939 (1932).

[19] LADENBURG, *Ber.*, **18**, 2956 (1885); **19**, 780 (1886).

[20] PRELOG and SCHÖNBAUM, *Ann.*, **545**, 256 (1940).

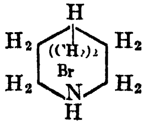
ammonia or a primary amine and ethyl β-bromopropionate, itself made by addition of hydrobromic acid to ethyl acrylate. The β-amino diester may also be formed through union of a β-bromo-with a β-amino-propionate, the latter compound being formed by bromination of succinimide[21] (Hofmann reaction with sodium hypobromite) and subsequent esterification by alcohol and hydrochloric acid.

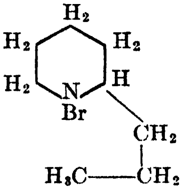
Finally, several fragments may be put together simultaneously,[22] as seen in the following scheme:

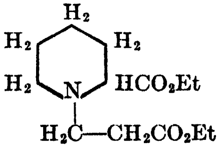


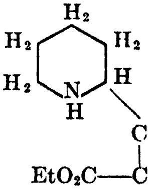
This procedure is somewhat reminiscent of the Hantzsch synthesis (page 187), except that one keto diester is condensed with two aldehydes and an amine instead of two keto esters with one aldehyde and an amine.

Synthesis of Bicyclic Compounds.—Bicyclic compounds may be constructed by the addition of an extra ring to a piperidine system or by the simultaneous closing of two rings. Several compounds in which a second ring can be formed are shown below.









In the first[23] and second,[24] a conventional splitting of hydrogen halide under the influence of heat, alkali, or sulfuric acid occurs; in the third, sodium in boiling toluene effects a condensation like that which occurs in the preparation of ethyl acetoacetate from ethyl acetate, but the process in this case is known as the Dieckmann reaction;[25] in the fourth,[26] ring closure takes place when the ester is reduced catalytically over nickel. These reactions can be used to make additional rings with one, two, or three methylenes in the chain and to connect the nitrogen with other carbon atoms of the ring. The necessary intermediates are usually derived from pyridine by conventional steps as will be illustrated later in the synthesis of quinuclidine (page 255).

---

[21] HALE and HONAN, *ibid.*, **41**, 770 (1919).

[22] PETRENKO-KRITSCHENKO, *J. prakt. Chem.* [2], **85**, 1 (1912); PETRENKO-KRITSCHENKO and ZONEFF, *Ber.*, **39**, 1358 (1906); *cf.* MANNICH, *Arch. Pharm.*, **273**, 323 (1934).

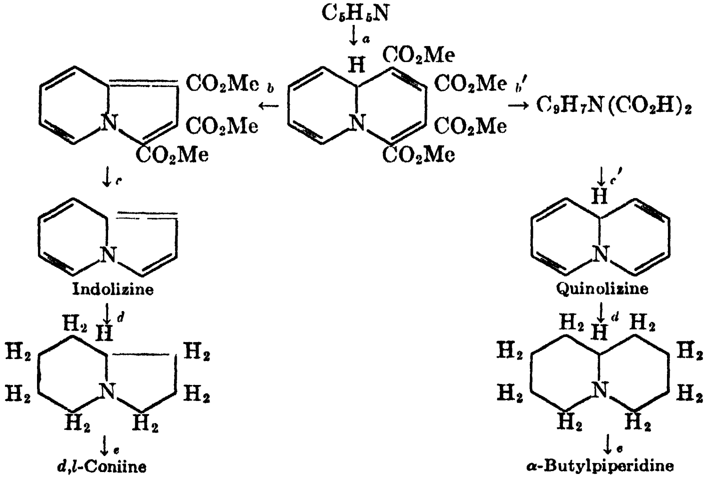
[23] LÖFFLER and STIETZEL, *Ber.*, **42**, 124 (1909); MEISENHEIMER, NERESHEIMER, and SCHNEIDER, *Ann.*, **420**, 190 (1920).

[24] HOFMANN, *Ber.*, **18**, 109 (1885); LÖFFLER and KAIM, *ibid.*, **42**, 94 (1909).

[25] CLEMO and RAMAGE, *J. Chem. Soc.*, 437 (1931); CLEMO, RAMAGE, and RAPER, *ibid.*, 2959 (1932).

[26] TULLOCK and MCELVAIN, *J. Am. Chem. Soc.*, **61**, 961 (1939).

Another method for making a second ring is to add ethyl acetylenedicarboxylate to pyridine, a variation of the well-known Diels-Alder[27] reaction. The remaining steps employed in this synthesis are shown in Fig. 1. Included in the diagram also is the action of cyanogen bromide on the two bicyclic systems. This reagent incidentally, proves the point of attachment of the second carbon ring; for one ring is opened and an α-substituted piperidine is formed. This Diels-Alder reaction is therefore applicable to the preparation of alkyl substituted piperidines as well as of bicyclic systems.



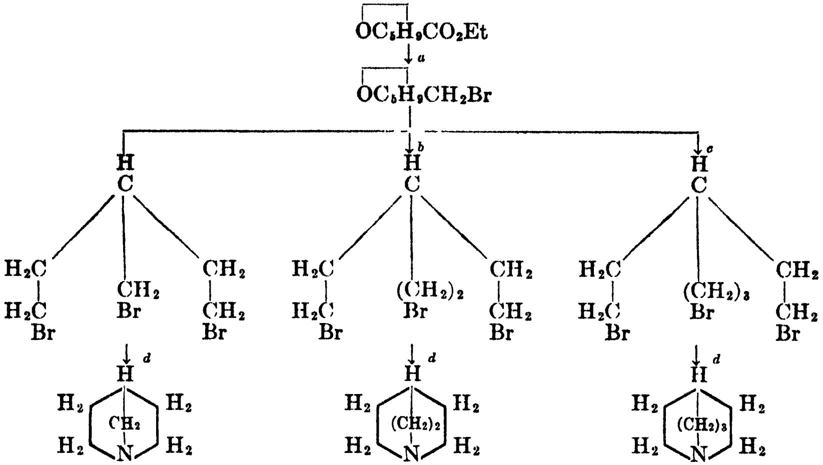
[a] $MeO_2CC \equiv CCO_2Me$. [b] Distillation with dilute HNO_3 or treatment with $Na_2Cr_2O_7$. [b'] Hydrolysis with boiling HCl. [c] KOH, HCl, and heat. [c'] Distillation with CaO. [d] $H_2 + PtO_2$ in CH_3CO_2H. [e] BrCN, H_2 + Pd.

FIG. 1.—Preparation of bicyclic compounds by addition of methyl acetylenedicarboxylate to pyridine.

Simultaneous closing of two rings occurs when an appropriate tribromo compound is heated with methyl alcoholic ammonia. Figure 2 illustrates a series of transformations whereby ethyl tetrahydropyrane-4-carboxylate (see Fig. 3) is converted[28] to three members of an homologous series. The general process consists (*a*) of changes on the side chain of the tetrahydropyrane compound, (*b*) of ether scission (ring opening) by means of strong hydrobromic acid, and (*c*) of ring closure to the bicyclic compound by use of hot alcoholic ammonia.

[27] DIELS, ALDER, *et al.*, *Ann.*, **498**, 16 (1932).

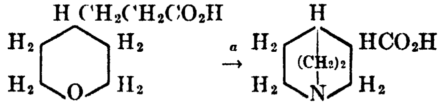
[28] (*a*) PRELOG and CERKOVNIKOW, *ibid.*, **525**, 292 (1936); **532**, 83 (1937); (*b*) PRELOG, KOHLBACH, CERKERNIKOW, REZEK, and PIANTANIDA, *ibid.*, **532**, 69 (1937).



[a] Na + EtOH, HBr. [b] KCN, H_2O + HX, EtOH + HX, Na + EtOH, HBr 45 per cent.
[c] $NaCH(CO_2Et)_2$, saponification and decarboxylation, EtOH + HCl, Na + EtOH, HBr 45%.
[d] Methyl alcoholic ammonia (20 per cent) at 130 to 140°.

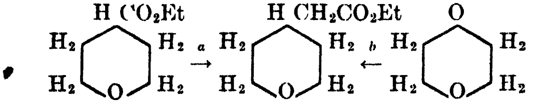
FIG. 2.—Conversion of γ-carbethoxytetrahydropyrone to 1-azabicyclo [2.2.1] heptane, quinuclidine, and 1-azabicyclo [3.2.2] nonane.

β-Tetrahydropyranylpropionic acid, which is formed in one of the foregoing steps in Fig. 2c, can be converted to quinuclidine -2-carboxylic by the following sequence:



[a] Fuming HBr to open the ring, Br_2 + red P, CH_3OH + NH_3 at 135°.

Figure 3 shows a variety of methods[28b] for preparing tetrahydro pyranyl-4-acetic acid, which is employed as an intermediate in the preparation of these bicyclic compounds.



Sequence of Reagents and Reactions

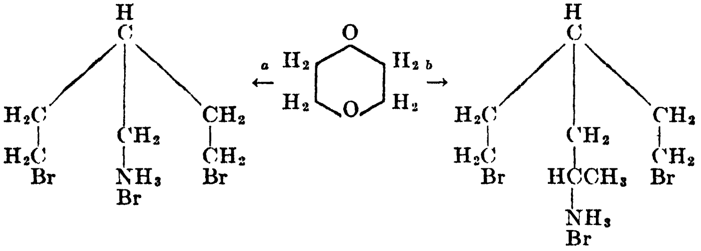
[a] The starting material is prepared from the reaction $O(CH_2CH_2Cl)_2$ + $Na_2C(CO_2Et)_2$ followed by saponification, partial decarboxylation, and esterification. The sequence of reagents for chain lengthening is; Na + EtOH, PBr_3 + pyridine, KCN, KOH, HX + EtOH.

[b] Zn + $BrCH_2COOEt$(Reformatsky reaction) dehydration with Ac_2O to yield unsaturated product, catalytic hydrogenation. Another suitable process is condensation with $H_2C(CN)COOEt$ in the presence of pyridine, hydrolysis of ester and loss of CO_2, EtOH-H_2SO_4 in order to esterify the nitrile, reduction of double bond by H_2 over PtO_2.

A third path from γ-pyrone is by reduction by H_2 + colloidal Pt-black, formation of ester with $C_6H_5SO_2Cl$, ethyl sodiomalonate, hydrolysis, decarboxylation of one carboxyl group, esterification of the other carboxyl group.

FIG. 3.—Methods for the preparation of ethyl tetrahydropyranylacetate.

If two of the arms contain bromine atoms and the third holds an amino group, an intermolecular alkylation[29] occurs under the influence of alkali with formation of a bicyclic system. Methods for preparing such intermediates from γ-tetrahydropyrone are shown in Fig. 4.



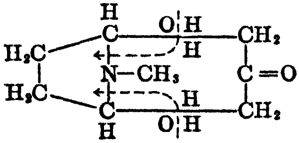
[a] Zn + $BrCH_2CO_2Et$ (Reformatsky reaction), Ac_2O + 2 drops H_2SO_4 to remove water from carbinol, $H_2 + PtO_2$ to reduce the double bond, NaOH to saponify the ester, HX to recover the acid, NaN_3 to form the amine by the Curtius-Schmidt reaction, HBr to form the ammonium salts, fuming HBr to open the ring and form the dibromo ammonium bromide compound.

[b] Zn + $BrCH_2CO_2Et$, $Ac_2O + H_2SO_4$, $H_2 + PtO_2$, $SOCl_2$ to form the acid chloride, MeZnX, $H_2NOH + Na_2CO_3$ to form the oxime, Na + abs. EtOH to reduce the oxime to an amine, HBr to form the ammonium salt, fuming HBr to open the ring.

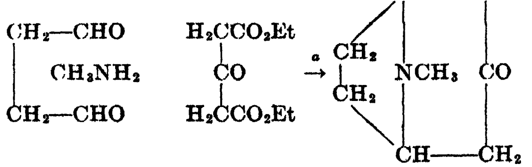
Ring closure to the bicyclo compound occurs with 50 per cent KOH.

FIG. 4.—Methods for the preparation of amino dibromides which can be used to form azabicyclic compounds.

Robinson's synthesis provides a general method for the simultaneous closure of two rings and formation of a bicyclic compound with a nitrogen atom as the bridge. Robinson[30] perceived that an imaginary hydrolysis



would cleave tropinone to succinaldehyde, methylamine, and acetone. He accordingly condensed succindioxime with methylamine and acetone and obtained a small yield of tropinone. Substitution of ethyl or calcium acetonedicarboxylate for acetone materially improved the process and gave the dicarbethoxy or dicarboxylic acid which by an easy hydrolysis and decarboxylation yielded tropinone.



Mixture allowed to stand overnight.

---

[29] (a) PRELOG, HEIMBACH, and RAZEK, *ibid.*, **545**, 231 (1940); (b) PRELOG, HEIMBACH, and CERKOVNIKOW, *ibid.*, **545**, 243 (1940).

[30] ROBINSON, *J. Chem. Soc.*, **111**, 762 (1917).

The biogenic[31] possibilities of this condensation are shown by the effect of temperature and of different pH values on the yield (see Table II).

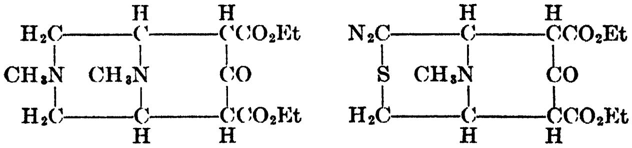
TABLE II.—FORMATION OF TROPINONE FROM SUCCINDIALDEHYDE, ACETONE DICARBOXYLIC ACID, AND METHYL AMINE CHLOROHYDRATE IN A BUFFERED SOLUTION. TIME 3 DAYS.

pH at beginning	..	3.0	5.0	7.0	9.0	11.0	13.0
pH at end	I[a]	3.0	5.1	7.0	8.6	11.0	12.6
	II[b]	3.3	6.0	7.0	8.2	10.7	13.6
Yield, per cent	I[a]	47	54	65	66	86	3
	II[b]	68	83	78	61	84	5

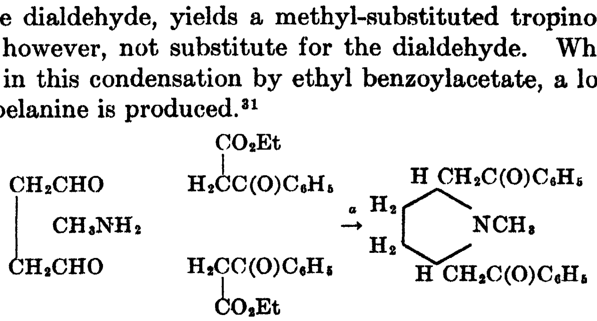
[a] Temperature 25°.
[b] Temperature 20°.

This elegant synthesis is capable of wide and unique application[32] by variation of the dialdehyde, the amine, or the compound with the active methylene group. For example, the longer chain dialdehyde, adipaldehyde (from cyclohexene via the chloro hydrate, the diol, and oxidation with lead tetraacetate) yields a homologue of tropinone known as N-methylhomogranatonine.

Glutaraldehyde yields pseudopelleterin in 72 per cent yield at a pH 7, a temperature of 25°, and a period of 8 days.[31] The acetal,[32] $CH_3N(CH_2CH_2(OEt)_2)_2$, obtained from methylamine and bromodiethylacetal, $BrCH_2CH(OEt)_2$, condenses as if it were a dialdehyde and yields N-methylazadicarbethoxytropinone, *i.e.*, 6, 8-dicarbethoxy-7-oxo-3,9-diethyl-3,9-diazabicyclo [3.3.1] nonane.



Parallel changes with a sulfur or selenium diacetal lead eventually to a thio- or seleno-tropinone, respectively. Levulinic aldehyde, used in place of the dialdehyde, yields a methyl-substituted tropinone. Diketones will, however, not substitute for the dialdehyde. When acetone is replaced in this condensation by ethyl benzoylacetate, a lower homologue of lobelanine is produced.[31]



[a] Condensation, hydrolysis, decarboxylation.

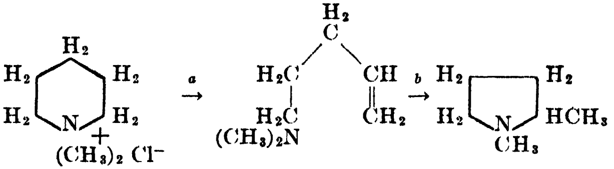
---

[31] SCHÖPF and LEHMAN, *Ann.*, **518**, 1 (1935).

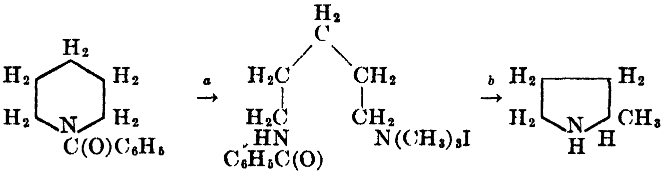
[32] (*a*) MENZIES and ROBINSON, *J. Chem. Soc.*, **125**, 2163 (1924); (*b*) BLOUNT and ROBINSON, *ibid.*, 1429 (1932); 1511 (1933).

If the dialdehyde is replaced by 2 molecules of an aldehyde, the process becomes the same as that already mentioned (page 235) for preparing piperidones. The synthesis is, therefore, one that is broadly applicable to mono- or bi-cyclic systems as long as there are two aldehyde groups or their equivalent, two active methylene groups (in some cases only one active hydrogen), and one primary amine. The process is also related to the Mannich reaction.

Reactions of Piperidines.—Considerable interest in the chemical behavior of piperidine compounds centers in the cleavages that make opening of the ring and formation of new compounds possible. For example, the ring may be converted to an unsaturated amino compound which then can be changed to an α-substituted pyrrolidine by way of the ammonium salt[33] or benzoyl derivative[34] as shown below. The reactions are of the type already mentioned in an earlier chapter.

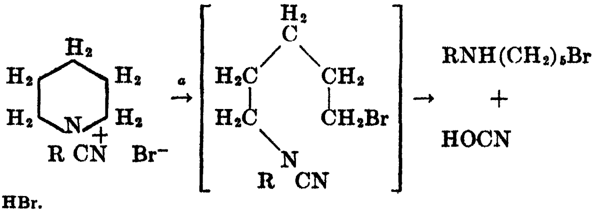


[a] NaOH and heat. [b] Addition of HCl to the double bond, NaOH closes the ring, heat causes loss of CH_3Cl.



[a] PCl_5, NaI, $(CH_3)_3N$. [b] Ag_2O causes the formation of $C_6H_5C(O)NH(CH_2)_3CH{=}CH_2$ together with some dimethylaminobenzamide, HCl, at 70° forms δ-chloroamylbenzamide, NaOH causes formation of the five-membered ring.

Cyclic bases that contain a tertiary nitrogen atom are in general attacked by cyanogen bromide or chloride. The reaction may proceed by formation of an addition compound which then undergoes hydrolysis with scisson of a carbon-nitrogen bond. If this bond is in the ring, an open-chain aminobromo compound results; if outside



[a] 48 per cent HBr.

---

[33] Hofmann, *Ber.*, **14**, 659 (1881); Merling, *Ann.*, **264**, 310 (1891).

[34] v. Braun, *Ber.*, **43**, 2864 (1910).

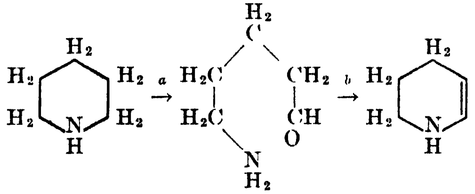
the ring, the piperidine nucleus remains intact, as shown below:

$$C_5H_{10}N{\cdot}R \rightarrow C_5H_{10}N^{+}{\cdot}(R)CNBr \rightarrow C_5H_{10}N{\cdot}CN + RBr$$

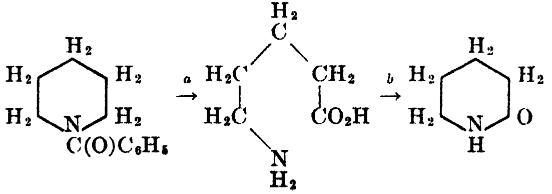
This reaction[35] is general for all tertiary amines, whether or not in a ring system, and the tendency for elimination of a radical as RBr without ring opening decreases as R is an allyl, benzyl, methyl, ethyl, propyl, isopropyl, or phenyl group. In other words, the ease of opening a ring is greatest with N-phenylpiperidine and least with N-alkylpiperidine.

Bicyclic systems with the nitrogen attached to both rings are converted to substituted piperidines by this reagent. Such application has already been mentioned (Fig. 1). The bromocyanide product may also be reduced catalytically to an aminoalkane in methyl alcoholic potassium hydroxide.[36] When the cyanide is treated with concentrated hydrochloric acid, the corresponding chloride salt forms.

Oxidizing agents readily attack the piperidine nucleus. Hydrogen peroxide[37] converts it to an aminovaleraldehyde, and permanganate[38] changes benzoylpiperidine to α-aminovalerianic acid. Both products are convertible again to ring structures by dehydration.



[a] 3% H_2O_2. [b] Dehydration.



[a] $KMnO_4$. [b] Dehydration.

Reduction with hydriodic acid[39] at 300° eliminates nitrogen from piperidine and forms the corresponding aliphatic hydrocarbon.

2-Methyl-Δ^2-tetrahydropyridine has a carbon-nitrogen link of the type $-\underset{|}{C}=\underset{|}{C}-NH-$,which is broken with extreme ease. For example, the application of a Schotten-Baumann reaction causes ring opening with formation of the benzoylated amino ketone.[40] This change bears some resemblance to that which occurs in the imidazole series where another

---

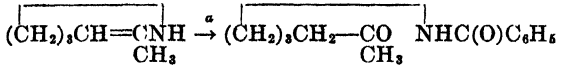
[35] v. **Braun**, *ibid.*, **40,** 3914, 3933 (1907).

[36] **Winterfeld** and **Holschneider**, *ibid.*, **64,** 137 (1931); *cf.* Ref. 27.

[37] **Wolffenstein**, *ibid.*, **25,** 2777 (1892); **26,** 2991 (1893).

[38] **Gabriel**, *ibid.*, **22,** 3335 (1889); **23,** 1767 (1890).

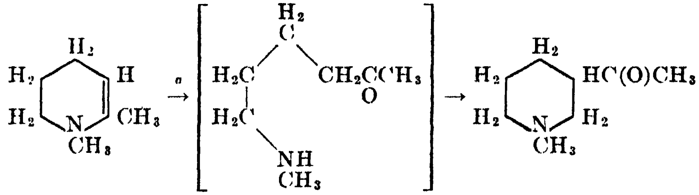
[39] **Spindler**, *J. Russ. Phys. Chem. Soc.*, **23,** 40 (1891); *J. Chem. Soc.*, **64,** 174 (1893).



$$(\mathrm{CH_2})_3\mathrm{CH{=}}\underset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{NH} \xrightarrow{a} (\mathrm{CH_2})_3\mathrm{CH_2{-}}\underset{\mathrm{CH_3}}{\mathrm{CO}}\quad \mathrm{NHC(O)C_6H_5}$$

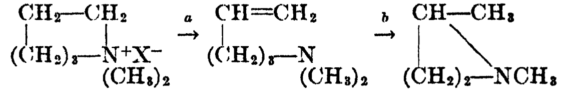
a $NaOH + C_6H_5C(O)Cl$.

vinyl amine system exists (see Chap. 13). Equally remarkable are the changes that occur when the N-methyl derivative of this tetrahydro piperidine is treated with aqueous formaldehyde at 0°. The ring apparently opens, and the resulting ketone seems to undergo an intramolecular Mannich reaction with formaldehyde. The product is a β-acetylpiperidine[41] (see below).



a $H_2CO + H_2O$.

Proof of this structure is given by reduction (sodium and alcohol) of the ketone to an alcohol, elimination of water (hydrochloric acid), and reduction (tin and hydrochloric acid) of the vinyl derivative. The product is identical with that prepared by reduction of β-ethylpyridine and methylation of the product.[41a] When dimethylpiperidinium halide is heated until the ring is cleaved and the product is treated with hydrochloric acid, a dimethylpyrrolidine results. Besides the value which these



a Heat. b HCl, NaOH.

methods of ring opening have in the determinations of structures, they are very useful for synthesis of open-chain compounds. The products may be alkanes, 1,5-dihalo compounds, halogen amino compounds, unsaturated amines, amino aldehydes and ketones, depending on the reagent used. Such reactions illustrate once again the way in which heterocyclic systems can be used for preparing nonheterocyclic compounds.

Apart from these numerous examples of ring opening, piperidines have the usual reactions of a secondary amine. The ease with which the parent compound can be obtained pure causes it to be used in a large number of reactions in which any other secondary amine might serve equally as well.

---

[40] Lipp, *Ann.*, **289**, 173 (1896).

[41] (*a*) Lipp and Widnmann, *Ber.*, **38**, 2276, 2471 (1905); *Ann.*, **409**, 96 (1915); (*b*) Stoehr, *J. prakt. Chem.* [2], **43**, 153 (1890); **45**, 20 (1892).

Piperidine Compounds.—*Piperidine,* the simplest member of this group, boils at 106° and freezes at −9°. It has a strong odor and affects the central nervous system. It is a stronger base than pyridine. It is commonly prepared by reduction of pyridine but can be synthesized by several of the methods already described.

Piperidine has a wide number of uses in the laboratory. It is an effective catalyst in many condensations where water must be split from reagents. The Knoevenagel reaction described in the previous chapter (page 187) is an example of its ability to effect a union of molecules where the use of a primary amine would have caused the condensation to have progressed to the pyridine state. As a reagent[42] for splitting hydrogen halide from a molecule, it is superior in many cases to alcoholic ammonia, aromatic amines, alkali hydroxides, etc., and the product of such reaction is less apt to be contaminated with by-products.

Piperidine, like organic bases and phenols, has a marked effect in preventing oxidation[43] of synthetic rubbers. It also promotes combination of more sulfur during vulcanization. Piperidinium pentamethylene dithiocarbamate, made by the action of piperidine on carbon disulfide, is more convenient to use because it serves as a solid equivalent of piperidine. In the presence of zinc oxide, the piperidinium compound is, in fact, even better than piperidine and causes vulcanization at least twenty-five times as fast.

Piperidine is an excellent agent for the preparation of derivatives[44] of aromatic halogen nitro compounds where the halogen is ortho- or para- to the nitro group and, therefore, sufficiently labile to be replaced by the piperidino radical. Labile nitro groups may be similarly displaced.[42]

Piperidine is also used frequently as a condensing agent in the Mannich reaction. Its role is that of any secondary amine that facilitates the union of a compound with an active hydrogen atom, such as is present in methyl phenyl ketones, with formaldehyde.

$$\mathrm{RH + H_2CO + HNC_5H_{10} \xrightarrow{HCl} R{-}CH_2{\cdot}NC_5H_{10}{\cdot}HCl + H_2O}$$

Homologues of piperidine are given names that suggest the common names of the pyridine compounds from which they are derived. For example, α-, β-, or γ-pipecoline refers to hexahydro-α-, -β-, or -γ-picoline. Similarly, lupetidine means hexahydrolupidine. Copellidine is the hydrogenated copelline. Parpevoline is from a parvoline. Conyrine (2-propylpiperidine) is the hydrogenated coniine.

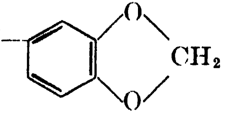
---

[42] Le Fèvre and Turner, *J. Chem. Soc.*, 1113 (1927).

[43] Whitby and Katz, *Ind. Eng. Chem.*, **25**, 1204, 1338 (1933).

[44] Seikel, *J. Am. Chem. Soc.*, **62**, 751 (1940); *cf.* Ref. 42.

Piperine, $C_{17}H_{19}O_3N$ (m.p. 128 to 129.5°), $C_5H_{10}N{\cdot}C(O)CH =$ CHCH=CH—



occurs to the extent of 5 to 9 per cent in white and black commercial pepper. It is an amide of piperic acid.[45] Permanganate oxidation of this acid yields piperonal, $CH_2O_2{\cdot}C_6H_3CHO$, and on further oxidation piperonylic acid, $CH_2O_2{\cdot}C_6H_3COOH$, the structure of which is proved by its synthesis from methylene iodide and protocatechuic acid, $(HO)_2C_6H_3COOH$. Preparation of piperic acid starts with protocatechuic aldehyde, $(HO)_2C_6H_3CHO$, and by means of methylene iodide and potassium hydroxide progresses to piperonal, from thence to piperonal acrolein, $CH_2O_2{\cdot}C_6H_3CH{=}CH{-}CHO$, by condensation with acetaldehyde in the presence of dilute alkali, and finally to piperic acid by a Perkin condensation with acetic anhydride and sodium acetate. The amide is then made from the acid chloride and piperidine.

Natural pepper contains chavicine also which is a cis-cis isomer of piperine. The natural peppery compounds are principally amides in which the acid radical is unsaturated and the nitrogen-containing portion is piperidine. Saturation of an acid radical may eliminate the pepper taste. Synthetic products are constructed on this general principle.[46] Undecylenic, isodecylenic, decanoic, nonanoic, and piperonylic acids are outstandingly effective. A cis arrangement as in chavicine (cis-cis) is better than the isomeric trans as in piperine (trans-trans). Isobutylamine, vanillylamine, and piperidine are amino components found in natural products. The synthetic piperazine can replace piperidine. According to Staudinger, a peppery taste is best obtained with derivatives of δ-phenylvaleric acid. In the first World War, synthetic peppers were made by impregnating powdered clay or nut shells with a synthetic piperidide made from the reaction of piperidine with the acid chloride of 5-phenyl-2-pentenoic or 5-phenyl-3-pentenoic acid.

Coniine and the Hemlock Alkaloids.—The five hemlock alkaloids are of special interest not alone because the ancient Greeks administered the death penalty with hemlock juice but also because Ladenburg, in 1886, synthesized coniine, which was the first optically active natural alkaloid to be prepared in the laboratory. Although the preparation is now considered a very simple one, the study of these alkaloids laid the ground work for much of the present-day knowledge of pyridine and piperidine chemistry.

---

[45] LADENBURG and SCHOLTZ, *Ber.*, **27**, 1958 (1894); RÜGHEIMER, *ibid.*, **15**, 1390 (1882).

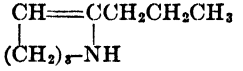
[46] SANDERMANN, *Seifensieder Ztg.*, **68**, 41 (1941); *C.A.*, **35**, 2995 (1941).

Coniine, with other related alkaloids, is found in all parts of the plant (*Conium masculatum*).[47] The percentage is highest in the partially ripened fruit of the two-year old plant, where the content may reach 0.8 per cent. The finely ground seeds, well moistened with 15 per cent caustic soda, are extracted with ether. The ether solution is acidified with acid, the ether evaporated, and the solidified fat removed from the cooled mixture. Coloring matter is separated from the aqueous solution by extracting with ether. Strong (35 per cent) sodium hydroxide is then added, the alkaloids are extracted with ether and are recovered by fractionation.

Crystals of coniine were first obtained[48] as early as 1827. The structure was suggested by Hofmann[49] who determined its molecular weight, obtained conyrine, now known as α-propylpyridine, by zinc-dust distillation, and oxidized conyrine to α-picolinic acid, thus establishing the position of the propyl group. Ladenburg's[50] synthesis consists of the condensation of α-picoline with paraldehyde by means of zinc chloride at 250°, reduction with sodium and alcohol, and resolution into the natural *d* form with tartaric acid. The condensation at 250° was later improved by making it stepwise, first to the hydroxyl compound $C_5H_4N{\cdot}CH_2CH(OH)CH_3$ at 150° and thence to the olefin at 185° for 10 hr. with hydrochloric acid. Some 2-chloropropylpyridine is formed as well. Both products are reduced with sodium and alcohol.

Coniine[51] is a colorless, oily liquid that boils at 166 to 167° and solidifies to a soft crystalline mass at $-2°$. It is optically active ($[\alpha_D] + 15.7°$), has a mousy odor, and darkens on exposure to light. It is very poisonous and produces paralysis of the motor-nerve terminations as well as other effects.[52] Its lethal activity is due to respiratory paralysis. N-methyl coniine, $C_9H_{19}N$, occurs in hemlock in both the *d* and *l* forms and results from methylation of coniine with methyl sulfate[53] or formaldehyde and formic acid.[54]

The optically inactive γ-conicëine (b.p. 171 to 172°), $C_8H_{15}N$, has the structure



$$\begin{array}{l} CH{=}CCH_2CH_2CH_3 \\ \;| \qquad\; | \\ (CH_2)_3{-}NH \end{array}$$

It can be derived from coniine by bromination and treatment with alkali.[24] The conventional synthesis of tetrahydropyridines is applicable to its preparation from α-phthalimidobutyl propyl ketone.[55] The compound is claimed to be eighteen times more active than coniine.[51]

---

[47] Chemnitius, *J. prakt. Chem.* [2], **118**, 25 (1928).

[48] Giesecke, *Arch. Pharm.*, **20**, 97 (1827).

[49] Hofmann, *Ber.*, **14**, 705 (1881); **18**, 5109 (1885).

[50] Ladenburg, *ibid.*, **19**, 439, 2578 (1886); **39**, 2486 (1906); **40**, 3734 (1907).

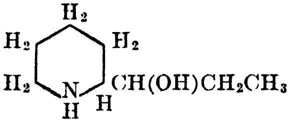
[51] "The Merck Index," Merck and Co., Rahway, N. J.

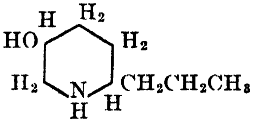
[52] Henry, "Plant Alkaloids," The Blakiston Company, Philadelphia, 1939.

[53] Passon, *Ber.*, **24**, 1678 (1891).

[54] Hess and Eickel, *ibid.*, **50**, 1386 (1917).

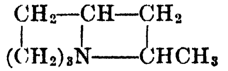
The two oxygenated hemlock alkaloids are *conhydrine*[56] and *pseudoconhydrine*,[57] both with the formula $C_8H_{17}NO$ and with the following probable constitutions:


Conhydrine


ψ Conhydrine

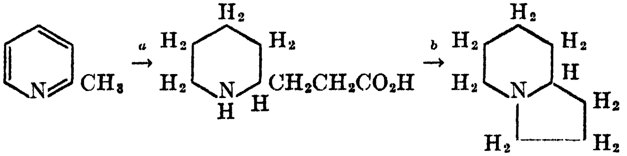
Chemical action on coniine and its related alkaloids has produced a number of isomeric compounds of the composition $C_8H_{15}N$. These substances are called *coniceines*[58] and are distinguished as α, β, γ, δ, ε, and ψ, largely according to the order of their discovery.

γ-*Coniceine*, as already mentioned, occurs naturally. Fuming hydrochloric acid at 220° produces the α-, β-, and γ- isomers from conhydrine.[59] The α-isomer has been considered both a mixture and the stereoisomeric form of 2-methylconidine,[60] otherwise called ε-coniceine.



$$\begin{array}{l}\mathrm{CH_2{-}CH{-}CH_2} \\ \;\,|\qquad\;\, |\qquad\;\; | \\ \mathrm{(CH_2)_3N{-\!\!-\!\!-}CHCH_3}\end{array}$$

The β-isomer is 2-allylpiperidine, $C_5H_{10}N{\cdot}CH_2CH{=}CH_2$. 4-Coniceine[61] is derived by dehydration of 4-conhydrine. Inactive *δ-coniceine* (b.p. 161°, picrate m.p. 206°), also called piperolidine, can be prepared from α-picoline[62] by the sequence of steps shown below. Hofmann's synthesis, by bromination of coniine at −16°, followed by sulfuric acid at 140°, antedates the above method, but the structure of the product was not then known. Another method of preparation is given on page 235.



[a] CCl_3CHO, alc. KOH, Na + abs. alc. [b] Heat on water bath to form the amide, 2-piperolidone, by intramolecular condensation, Na + alcohol.

---

[55] GABRIEL, *ibid.*, **42**, 4059 (1909).

[56] SPÄTH and ADLER, *Monatsh.*, **63**, 127 (1933).

[57] SPÄTH, KUFFNER, and ENSFELLNER, *Ber.*, **66**, 591 (1933).

[58] HOFMANN, *ibid.*, **18**, 16, 27, 112 (1885).

[59] LÖFFLER and TSCHUNKE, *ibid.*, **42**, 929 (1909).

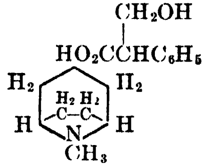
[60] LÖFFLER and FRIEDRICH, *ibid.*, **42**, 107, 946 (1909).

[61] LÖFFLER, *ibid.*, **42**, 946 (1909).

[62] LÖFFLER and KAIM, *ibid.*, **42**, 94 (1909).

Belladonna Alkaloids.—The belladonna group of alkaloids,[62] found in plants of the order Solanaceae, contains chiefly *l*-hyoscyamine and scopolamine with other minor alkaloids. *l-Hyoscyamine* is most abundant, but hydrolyzes readily to the *d,l* mixture, *atropine*, during extraction. Atropine is present in limited amounts in nature.

The piperidine structure of this alkaloid is emphasized in the accompanying formula. The other alkaloids, both natural and synthetic, in the group have this same basic structure but with changes on the carbon atom next to the phenyl group, on the 2,6-bridge across the piperidine ring, or at the nitrogen atom. Some of the variations are indicated in Table III.


Atropine

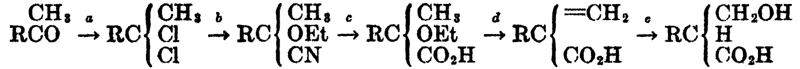
These drugs[63] have been known since early times. In fact, the name of the plant belladonna (beautiful lady) is a historical reminder that women of antiquity used a decoction in their eyes to dilate the pupils. The modern use is similar, though unrelated to beauty.

TABLE III.—ATROPINE AND RELATED COMPOUNDS

Substituent at carbon atom	Substituent on N atom	2,6-bridge	Common name
—CH_2OH..........	.CH_3	—CH_2CH_2—	Atropine
—CH_2OH..........	—CH_3	$-\overset{O}{HC\text{---}CH}-$	Hyoscine or scopolamine
—OH..............	—CH_3	—CH_2CH_2—	Homotropine[a]
—OH	—$CH_3 \cdot HBr$	—CH_2CH_2—	Novatropine[a]
—CH_2OH..........	—$CH_3 \cdot HNO_3$	—CH_2CH_2—	Eumadrine[a]
—OH..............	—CH_3	—CH_3 H_3C—	Eucotropine

[a] Atropine substitute, usually prepared from tropinone.

Concentrated hydrochloric acid at 130° or barium hydroxide at 60° cleaves atropine into tropine, $C_8H_{15}NO$, and tropic acid, $C_9H_{10}O_3$. The structure of *tropic acid* was readily solved and its preparation[64] from acetophenone effected in 1880 by the sequence of reactions shown below.



$$\overset{CH_3}{RCO} \xrightarrow{a} RC\begin{cases}CH_3\\Cl\\Cl\end{cases} \xrightarrow{b} RC\begin{cases}CH_3\\OEt\\CN\end{cases} \xrightarrow{c} RC\begin{cases}CH_3\\OEt\\CO_2H\end{cases} \xrightarrow{d} RC\begin{cases}=CH_2\\ \\CO_2H\end{cases} \xrightarrow{e} RC\begin{cases}CH_2OH\\H\\CO_2H\end{cases}$$

R = C_6H_5. [a] PCl_5. [b] KCN in EtOH. [c] H_2O. [d] Boiling conc. HCl. [e] HCl, K_2CO_3.

---

[63] GOODMAN and GILMAN, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

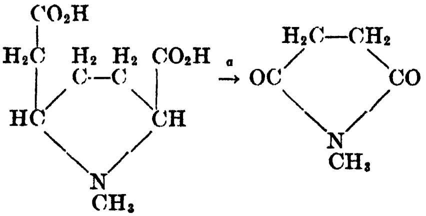
[64] LADENBURG and RÜGHEIMER, *Ber.*, **13**, 376, 2041 (1880).

The structure of *tropine* was much more difficult to solve. From the great number of degradations that necessarily accompany all efforts to determine structure, a few having the most direct bearing on the problem can be culled. (*a*) The presence of a pyridine nucleus[65] is shown by reduction of tropine with hydriodic acid at 140° to hydrotropidine, $C_8H_{15}N$, the chlorohydrate of which yields norhydrotropidine, $C_7H_{13}N$, when distilled, and this last compound, in turn, yields 2-ethylpyridine with zinc dust. (*b*) The presence of a secondary alcohol[66] is shown by oxidation with chromic acid to tropinone, $C_8H_{13}N$, which forms an oxime that reverts to tropine when treated with zinc dust and hydriodic acid. (Magnesium powder and strong hydrochloric acid yield, however, ψ-tropine.) (*c*) The presence of a tertiary nitrogen atom is shown by exhaustive methylation (CH_3I,KOH) which gives trimethyl amine from either tropidine or tropinone. (*d*) The presence of two active methylene[67] groups (system-$H_2C—CO—CH_2^-$) is indicated by the formation of a dibenzylidene derivative from tropinone. (*e*) The existence of a chain of seven carbon atoms[68] (which accounts for all the carbon atoms except that in the NCH_3 group), and the presence of double unsaturation where the MeN group has been extruded is shown by the following sequence:

$$\underset{\text{Tropine}}{C_8H_{15}NO} \xrightarrow{a} \underset{\text{Tropinic acid}}{C_8H_{13}NO_4} \xrightarrow{b} C_5H_6(CO_2H)_2 \xrightarrow{c} \underset{\text{Pimelic acid}}{HO_2C(CH_2)_5CO_2H}$$

[a] $CrO_3 + H_2SO_4$. [b] Exhaustive methylation. Trimethyl-amine and methanol are also obtained in this step. [c] NaHg.

(*f*) Presence of a five-membered ring system is shown by conversion of the tropinic acid, formed in the above sequence, to N-methyl succinimide.



[a] Concentrated chromic acid solution.

These conclusions were confirmed by the classical synthesis of Willstätter.[69]

---

[65] LADENBURG, *Ann.*, **217**, 117 (1883); *Ber.*, **20**, 1647 (1887).

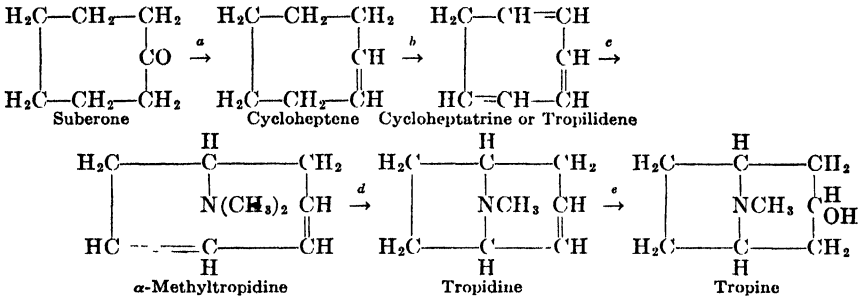
[66] (*a*) WILLSTÄTTER, *ibid.*, **29**, 393 (1896); (*b*) EICHENGRÜN and EINHORN, *ibid.*, **23**, 2870 (1890); (*c*) WILLSTÄTTER and IGLAUER, *ibid.*, **33**, 1174 (1900).

[67] WILLSTÄTTER, *ibid.*, **30**, 731, 2679 (1897).

[68] WILLSTÄTTER, *ibid.*, **28**, 3271 (1895); **31**, 1534 (1898); **34**, 129, 3163 (1901); *Ann.*, **317**, 204, 267, 307 (1901); **326**, 1, 23 (1903).

[69] WILLSTÄTTER, *Ber.*, **34**, 129, 3163 (1901); *Ann.*, **317**, 204, 267, 307 (1901); **326**, 1, 23 (1903).

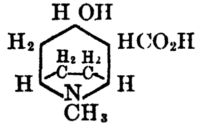
The 22 steps from suberone are summarized below. The series is interesting because of the great patience and skill required. By contrast, the great simplication in the preparation of members of this series effected by Robinson in his tropinone synthesis is more evident.

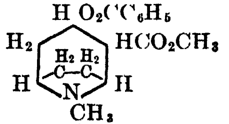

Suberone
Cycloheptene
Cycloheptatrine or Tropilidene
α-Methyltropidine
Tropidine
Tropine

[a] Hydroxylamine to form the oxime, reduction, exhaustive methylation. [b] Br_2, $HN(CH_3)_2$, exhaustive methylation, Br_2, treatment with quinoline. [c] HBr, $NH(CH_3)_2$. [d] 1,4-Reduction by sodium and alcohol, addition of bromine to the double bond, moderate heat to cause the formation of the second ring by ammonium salt formation, NaOH to eliminate HBr, CH_3I to form the iodide salt, AgCl to replace iodine by chlorine, heat to remove CH_3Cl. [e] Addition of HBr to double bond, hydrolysis of bromide by $H_2O + H_2SO_4$ to form ψ-tropine, oxidation by chromic acid to form tropinone, reduction by zinc dust Zn + HI at 0° to tropine. Pseudotropine is a stereoisomer of tropine.

Synthetic substitutes (Fig. 3) for atropine have, in general, the same general structure as atropine itself. Tropinone is a favorite starting point from which to obtain compounds of this class.

Cocaine and Related Compounds.—*Cocaine*, $C_{17}O_{21}O_4N$, is hydrolyzed to ecgonine which, in turn, is derived by treating the sodium salt of the enol form of tropinone with carbon dioxide (Kolbe synthesis) and then reducing the double bond with sodium amalgam.[70] The structure of cocaine is, therefore, apparent.


Ecgonine

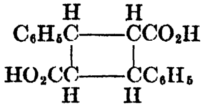

Cocaine

Cocaine is obtained from the leaves of *Erythroxylen coca* and related plants, found originally in Peru and Bolivia and cultivated in Java.[52] Besides cocaine, the plant contains other ecgonine esters, such as cinnamoylcocaine (methyl cinnamoylecgonine), which is apt to be present in younger leaves, and α- and β-truxilline (methyl α- or β-truxilloylecgonone) which are ecgonine esters of truxillic acid,[71] a compound with a ring of four carbon atoms which changes to cinnamic acid when distilled. Minor alkaloids are present also.

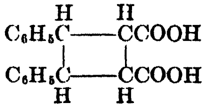
---

[70] WILLSTÄTTER and BODE, *Ber.*, **33**, 411 (1900).

[71] LIEBERMANN and DRORY, *ibid.*, **22**, 126, 682, 2254 (1889).



α-Truxillic acid.

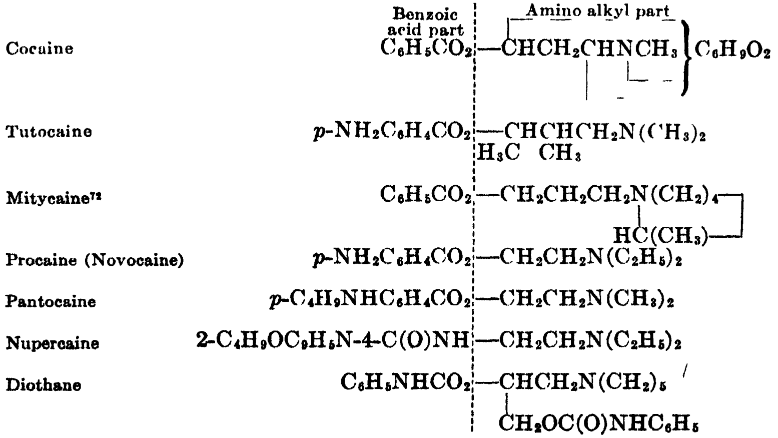


β-Truxillic acid.

Cocaine is used medicinally as a local anesthetic. The native Indian runners were accustomed to chew the leaves of the plant from which the alkaloid was obtained, because the alkaloid lessened hunger, by local action on the gastric mucosa, and increased endurance.[63]

Efforts to obtain a local anesthetic less toxic and with a longer period of anesthesia than cocaine have centered chiefly on the preparation of esters of benzoic or substituted benzoic acids in which the amino group of the alcohol is separated from the benzoyl radical by two or three carbon atoms similar to the $C_6H_5CO_2CCCN$-unit in cocaine.

Cocaine and a few substitutes are shown below.



	Benzoic acid part	Amino alkyl part
Cocaine	$C_6H_5CO_2$	$—CHCH_2CHNCH_3$ $C_6H_9O_2$
Tutocaine	p-$NH_2C_6H_4CO_2$	$—CHCHCH_2N(CH_3)_2$ $H_3C\ \ CH_3$
Mitycaine[72]	$C_6H_5CO_2$	$—CH_2CH_2CH_2N(CH_2)_4$ $HC(CH_3)$
Procaine (Novocaine)	p-$NH_2C_6H_4CO_2$	$—CH_2CH_2N(C_2H_5)_2$
Pantocaine	p-$C_4H_9NHC_6H_4CO_2$	$—CH_2CH_2N(CH_3)_2$
Nupercaine	2-$C_4H_9OC_9H_5N$-4-$C(O)NH$	$—CH_2CH_2N(C_2H_5)_2$
Diothane	$C_6H_5NHCO_2$	$—CHCH_2N(CH_2)_5$ $CH_2OC(O)NHC_6H_5$

These products are prepared by standard methods of esterification. *Novocaine*, for example, is derived from p-aminobenzoic acid, ethylene chlorohydrin, and diethylamine. The various piperidine radicals can be obtained easily by methods already described. The β-piperidylcarbinol in the last example is obtained from ethyl nicotinate by reduction with sodium and alcohol. The aminobenzoyl radicals are obtained by use of p-nitrobenzoylchloride during esterification, followed by catalytic reduction of the nitro group with the aid of platinum oxide. No definite relationship between physiological activity and structure appears to exist.[73,74]

---

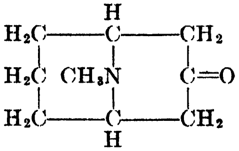
[72] (*a*) BAILEY and MCELVAIN, *J. Am. Chem. Soc.*, **52**, 1633 (1930); (*b*) WALTERS and MCELVAIN, *ibid.*, **55**, 4625 (1933).

[73] MCELVAIN, *ibid.*, **49**, 2835 (1927); *cf.* Ref. 72*a*.

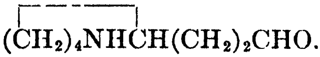
[74] SANDBORN and MARVEL, *ibid.*, **50**, 563 (1928); MARVEL and SHELTON, *ibid.*, **51**, 915 (1929).

Pelletierine and the Pomegranate-bark Alkaloids.—The root bark of the pomegranate tree contains *ψ-pelletierine*,[52] $C_9H_{15}ON$, and other alkaloids which are obtained after basification of the ground bark with slacked lime and extraction with chloroform. The root bark, and more particularly the mixed alkaloids in the form of "pelletierine tannate" and "pelletierine sulfate," are used as anthelmintics. The active principle is probably pelletierine, the name of which is derived from the French investigator on alkaloids, Pelletier.

The formula[75] for ψ-pelletierine, called also N-methylgranatonine, was arrived at by noting that its reactions and those of tropinone were so nearly parallel that the former must be the next higher homologue. Synthesis is accomplished by Robinson's method (see page 239).



Pelletierine, $C_8H_{15}ON$, boils at 106°/21 mm. It is isolated as the *d,l* mixture. The oxygen atom is in an aldehyde group whose oxime, with phosphorus pentachloride, yields a nitrile which in turn is hydrolyzed to the known β-2-piperidylpropionic acid and whose hydrazone, with sodium ethoxide at 156 to 170°, splits to *d,l* coniine. Pelletierine is therefore β-2-piperidylpropionaldehyde.[76]



$(CH_2)_4NHCH(CH_2)_2CHO$.

Arecoline and the Areca Nut Alkaloids.—*Arecoline* is the chief alkaloid in the areca (betel) nut. The seeds, mixed with lime and betel leaves, are widely used by the natives of East India in a masticatory mixture. Salivation is increased, the saliva is turned blood red, and the teeth are rapidly blackened. The chewer experiences a pleasing sensation of contentment. Craving for the drug becomes intense, but the habit is not degenerating.[77] The ground areca nut is used in India and China as a vermifuge, and in Europe for a similar purpose in veterinary medicine.

The compound is an odorless oil that boils at 209°. It is the methyl ester of 1-methyl-Δ^3-tetrahydropyridine-3-carboxylic acid. The relationship to nicotinic acid is shown by methylation of potassium nicotinate to give the N-methyl derivative of ethyl nicotinate, which in turn is reduced to a tetrahydro compound as well as a hexahydro product. The tetrahydro compound is optically inactive as is also the natural product.

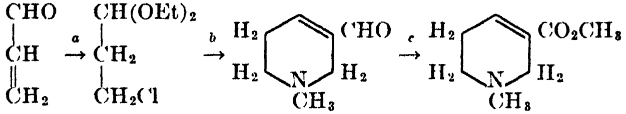
---

[75] CIAMICIAN and SILBER, *Ber.*, **25**, 1601 (1892); **26**, 159, 2740 (1893); **27**, 1851, 2860 (1894); **29**, 482 (1896); *Real Accad. Lincei* [V], ii, 219 (1899).

[76] HESS and EICHEL, *Ber.*, **50**, 1192 (1917).

[77] LEWIN, "Phantastica, Narcotic and Stimulating Drugs," E. P. Dutton & Company, Inc., New York, 1931; *cf.* Ref. 52.

Synthesis starts with acrolein and proceeds[78] by steps that parallel somewhat those for formation of β-carbethoxy-γ-pyridones, except for the use of the acetal instead of the ester and the employment of a different condensing agent.

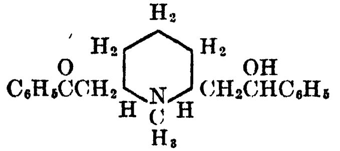


ᵃ HCl + EtOH. ᵇ H_2NCH_3 at 125 to 135°, cold fuming HCl to close the ring. ᶜ H_2NOH, dehydration, hydrolysis with HCl + H_2O, esterification by HCl + MeOH.

The acid derived by hydrolysis of arecoline is called arecaidine. *Guvacine* is Δ^3-tetrahydropyridine-3-carboxylic acid.

The Lobelia Alkaloids.—These compounds are found in the lobelia herb, which is known by many common names, such as Indian tobacco, emetic weed, asthma weed, bladder pod, or vomit wort. The chief alkaloid is *lobeline*, $C_{22}H_{27}NO_2$ (m.p. 130 to 131°). It is used as a respiratory stimulant.

Oxidation of lobeline with chromic trioxide in acetic acid yields the closely related lobelanine, $C_{22}H_{25}NO_2$. Nascent hydrogen converts both compounds to lobelanidine, $C_{22}H_{29}NO_2$. Lobelanine by zinc-dust distillation gives acetophenone; by a Beckmann rearrangement ($SOCl_2$) of its dioxime derivative, it yields the dianilide of lobelinic acid (1-methylpiperidine-2,6-diacetic acid); and by oxidation (chromic oxide and sulfuric acid), it gives 1-methylpiperidine-2,6-dicarboxylic acid (scopolinic acid). Exhaustive methylation (CH_3I, Ag_2O) yields, in one step, trimethylamine and a compound which, by hydrogenation with palladium black in acetic acid, gives 1,9-dihydroxy-1,9-diphenyl-*n*-nonane, or with the same catalyst in ethanol gives 1,7-dibenzoyl-*n*-heptane. These results are logically interpreted[79] on the basis that lobeline has the formula shown below and that lobelanine is the diketo product derived by oxidation of the secondary alcohol.



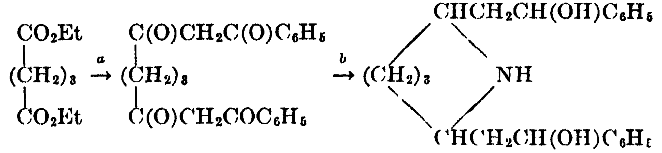
Synthesis[80] of compounds in this series begins with a condensation of ethyl glutarate with acetophenone by means of sodamide. The tetraketone then undergoes ring closure when treated with ammonia and the product is reduced readily in two steps to norlobelanidine. Robinson's method may also be used.[31]

---

[78] Wohl and Johnson, *Ber.*, **40**, 4712 (1907).

[79] Wieland and Draegendorff, *Ann.*, **473**, 83 (1929).

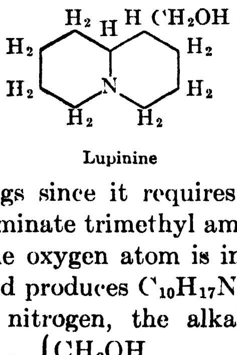
[80] Wieland and Drishaus, *ibid.*, **473**, 102 (1929).



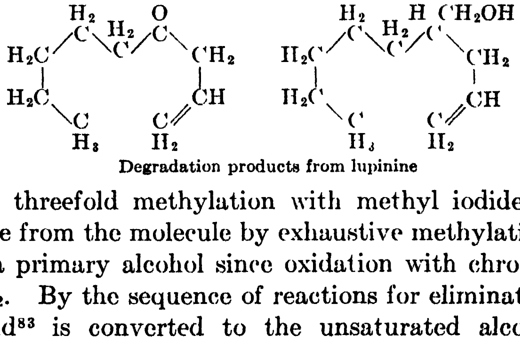
[a] $CH_3C(O)C_6H_5 + NH_3$. [b] NH_3 to form α- and β-norlobelanidine, reduction of the two carbonyl groups by H_2 over PtO_2, reduction of the two olefin bonds by NaHg in moist ether.

Lupine Alkaloids and Norlupinane. (Octahydroquinolizine).—The lupine alkaloids occur in plants of the genus *Lupinus angustifolius* of which the most common species is *L. albus.* The species *L. perennis* is commonly called sundial because the leaves turn toward the sun. The plants contain lupinine,[81] $C_{10}H_{19}ON$; sparteine, $C_{15}H_{26}N_2$; lupanine, $C_{15}H_{24}ON_2$; and hydroxylupanine. Lupanine occurs in the dextro and the inactive form in *L. albus*, and in the dextro form in *L. angustifolius.* The inactive variety can be readily isolated from *L. termis* which is native in North Africa and Syria.

The simplest member, *lupinine*, probably has the structure[82] shown below. The nitrogen atom is known to be tertiary and attached to both rings since it requires a threefold methylation with methyl iodide to eliminate trimethyl amine from the molecule by exhaustive methylation. The oxygen atom is in a primary alcohol since oxidation with chromic acid produces $C_{10}H_{17}NO_2$. By the sequence of reactions for elimination of nitrogen, the alkaloid[83] is converted to the unsaturated alcohol $C_7H_{14}\left\{\begin{matrix}CH_2OH\\CH{=}CH_2.\end{matrix}\right.$ Oxidation of this material gives a lactone $C_9H_{16}O_2$ which necessarily must be a δ- or γ-lactone. Therefore the CH_2OH group in the original alkaloid must have been in the delta or gamma position from the nitrogen atom. The unsaturated alcohol and its hydrogenated (H_2 + Pt) derivative are optically active. Conversion (PBr_5) of the saturated alcohol to the bromide and thence by reduction (zinc dust, alcohol, and a drop of platinic chloride) to the hydrocarbon, $C_7H_{14}\left\{\begin{matrix}CH_3\\CH_2{-}CH_3,\end{matrix}\right.$



Lupinine



Degradation products from lupinine

---

[81] Clemo and Leitch, *J. Chem. Soc.*, 1811 (1928).

[82] Willstätter and Fourneau, *Ber.*, **35**, 1910 (1902).

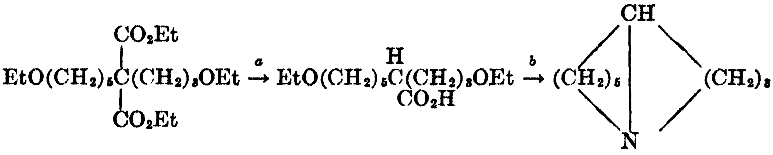
[83] Karrer, Canal, Zohner, and Widmer, *Helv. Chim. Acta*, **11**, 1062 (1928).

is accomplished with retention of optical activity; but formation of a trimethylammonium salt from the above bromide and from thence an unsaturated system by the customary degradation process destroys the optical activity. Hence the position of optical activity in the alkaloid must be on the carbon atom adjacent to the carbinol group. Ozonization of the last unsaturated compound yields a ketone that is optically inactive. A Beckmann rearrangement of the oxime derived therefrom then produces an acid amide that splits (HCl) to *n*-amyl amine and *n*-butyric acid. All these changes are understandable if the ketone and the original unsaturated alcohol are as shown, respectively, above. The possibility that one or both of the rings is five-membered with a methyl substituent on a carbon next to nitrogen is not excluded by this work, but the above arrangement is deemed more likely because it is similar to the ring system in the berberine alkaloids (page 319).

The parent ring of such a compound would be *octahydroquinolizine*, known also as *norlupinane*, octahydropyridocolone, or azabicyclo[4,4,0] decane. It can be prepared[25] from lupinine by chromic acid oxidation to lupininic acid and thence by decarboxylation of the hydrochloride over hot soda lime. The synthesis of norlupinane is of more than ordinary interest because of the variety of synthetic methods available, and because of an abnormal reduction that invalidated one of the attempts.

One of the successful methods has already been presented (page 236) as part of the reactions stemming from the addition of ethyl acetylenedicarboxylate to pyridine. Two others are given in Fig. 5.

If the keto compound in Clemo's synthesis is reduced by zinc and hydrochloric acid (Clemmensen's reduction) instead of by hydrazine sulfate, the product is not norlupinane, but the isomer, 1-azobicyclo-[5,3,0] decane.[84] The proof of the product from this very unusual change is given by the synthesis shown below.



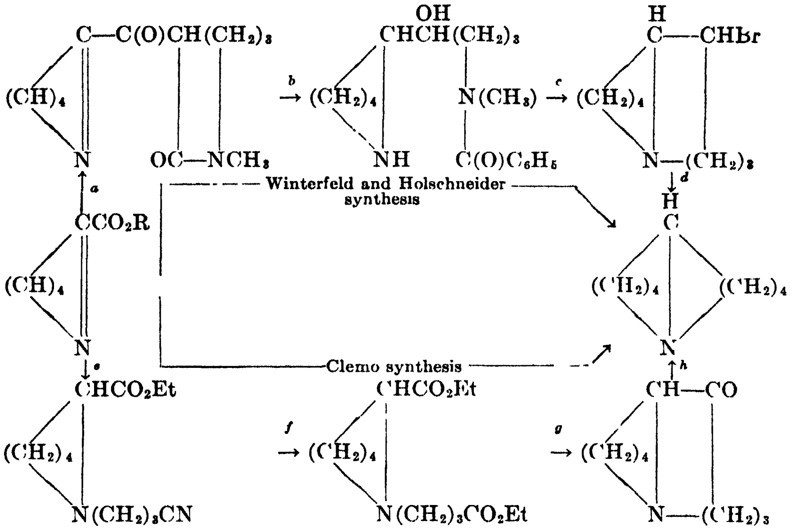
The starting material is made from ethyl malonate by successive reactions with $EtO(CH_2)_3Br$ and $EtO(CH_2)_5Br$.

[a] 50 per cent KOH, HX, heat. [b] Conc. $H_2SO_4 + NaN_3$ in $CHCl_3$, HBr, 60 per cent HBr at 100° for 3 hr.

The peculiarity exhibited in the above-mentioned Clemmensen reduction does not extend to all keto groups in bicyclic systems, for

---

[84] PRELOG and SEIWERTH, *Ber.*, **72**, 1638 (1939).



The starting material is prepared from α-picoline by permanganate oxidation and esterification. R = C_2H_5 in the Winterfeld and Holschneider synthesis; R = H in the Clemo synthesis.

Winterfeld and Holschneider synthesis.[85]

[a] Reaction with N-methylbutyrolactone and sodium ethoxide, in benzene solution.

[b] Fuming hydrochloric acid which opens the lactone ring and eliminates carbon dioxide, benzoylation with the Schotten-Baumann reaction, reduction with hydrogen and platinum oxide in acetic acid.

[c] Reaction with phosphorus pentabromide which eliminates the benzoyl group as benzonitrile and the methyl as methyl bromide (*cf.* page 240), ring closure with sodium ethoxide.

[d] Hydrogen in the presence of palladium on calcium carbonate in alcoholic potassium hydroxide.

Clemo synthesis.[86]

[e] Sodium in boiling amyl alcohol to reduce the ring, absolute alcohol with sulfuric acid to esterify, reaction with γ-bromobutyronitrile and anhydrous potassium carbonate.

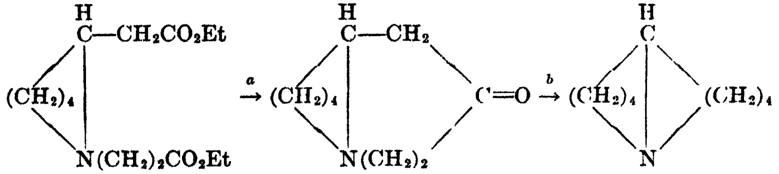
[f] Reaction in absolute alcohol saturated with dry hydrochloric acid

[g] Ring closure by reaction with finely divided sodium in toluene (Dieckmann reaction), 20 per cent sulfuric acid and heat to hydrolyze the ester and eliminate the carboxyl group.

[h] Wolff reduction.

FIG. 5.—Sequence of products in the synthesis of norlupinane.

the formation of norlupinane[85] from 2-ketoquinolizine shown below is normal.



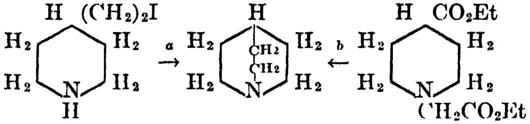
[a] Na in boiling toluene, acidification, and decarboxylation. [b] Zn + HCl.

Quinuclidine.—This compound, $C_{10}H_{13}N$ is the parent of the bicyclic system in the quina alkaloids. Like many others of its kind, it has a high melting point, 158°, and is very volatile. It has been synthesized in a number of ways, some of which have already been given on pages 235, 237. Two additional methods are outlined below.

---

[85] WINTERFELD and HOLSCHNEIDER, *Ann.*, **499**, 109 (1932).

[86] CLEMO, METCALFE, and RAPER, *J. Chem. Soc.*, 1429 (1936); *cf.* Ref. 25.



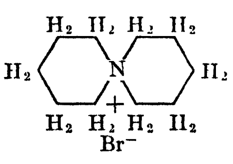
[a] The starting material is prepared from γ-picoline by condensation with H_2CO, reduction with Na and EtOH, conversion to the iodide with HI. [b] The starting material is prepared from β,γ-lutidine. The α-methyl group is eliminated by $KMnO_4$ followed by decarboxylation of the α-carboxyl group. Sodium and alcohol reduce the ring, alcohol and acid esterify the γ-carboxyl group, $ClCH_2CO_2Et$ + Na_2CO_3 complete the preparation of the starting compound. The steps to quinuclidine are made respectively (*a*) by heat and treatment with alkali and (*b*) by K in hot toluene followed by H_2NNH_2 + NaOEt at 175°.

The first is the original synthesis of Löffler and Stietzel,[23] which requires the somewhat inaccessible γ-picoline. The second[87] is based on the readily available β,γ-lutidine.

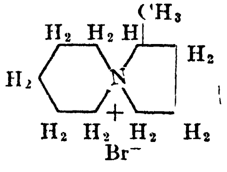
Homologues of quinuclidine are prepared by parallel changes from β-collidine or other pyridine compound.[88] 2-Chloromethylquinuclidine has a chlorine atom which, like some in the oxygen heterocyclic[89] series, is not removed by zinc and hydrochloric acid or by catalytic hydrogen.

Bispiperidinium Compounds.—When pentamethylene dibromide is treated with piperidine, an ammonium salt is produced according to the general reaction of this dibromide with secondary amines. The product in this instance is bispiperidinium bromide[90] (*A*).

A



B



This salt has the usual reactions expected of such a material. Silver oxide converts it to 5-piperidinopentene-1. The olefin will add hydrogen bromide (bromine to the 2-position), and this compound in turn with alkali changes to piperidinomethylpyrolidinium bromide (*B*).

Compounds of this type were useful for determining the stereochemical configuration of the ammonium ion.[91] Since *d,l*-4-phenyl-4′-carbethoxybispiperidinium-1:1′-spiran bromide can be resolved into optical isomers by means of the δ-α-bromocamphor-π-sulfonate, the ammonium ion must

---

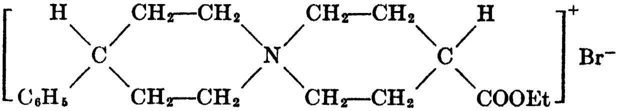
[87] Clemo and Metcalf, *J. Chem. Soc.*, 1989 (1937).

[88] Koenigs, *Ber.*, **37**, 3244 (1904); Koenigs and Bernhart, *ibid.*, **38**, 3049 (1905).

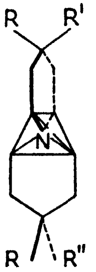
[89] Paul, *Bull. soc. chim.* [5], **2**, 747 (1930); Druey, *ibid.*, 2262.

[90] v. Braun, Müller, and Beschke, *Ber.*, **39**, 4347 (1906).

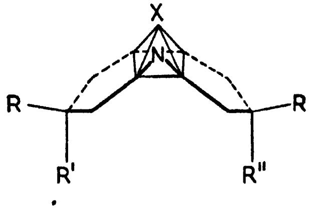
[91] Mills and Warren, *J. Chem. Soc.*, **127**, 2507 (1925).



have a tetrahedral configuration (*A*). If the nitrogen were pentavalent, the pyrimidal configuration (*B*) would possess symmetry and would be superimposable on the mirror image.



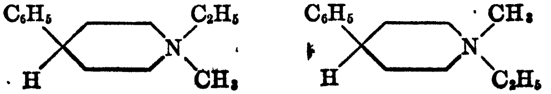
(*A*)



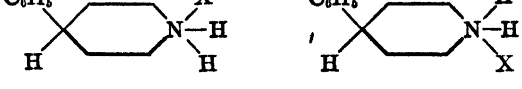
(*B*)

4-*Phenyl*-1-*methylpyridinium Salts*.—Another proof of the tetrahedral character of the ammonium ion[92] is furnished by the geometrical isomerism (*a*) of 4-phenyl-1-methyl-1-ethyl piperidinium iodide or perchlorate. If the nitrogen atom had had a pyrimidal structure (*b*), such isomerism

(*a*)



(*b*)



would have been observed even when two hydrogen atoms or two methyl groups were attached to nitrogen.

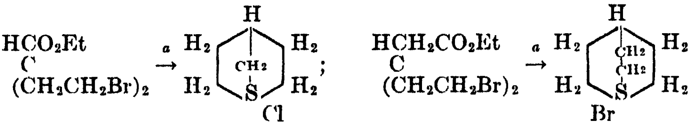
Bicyclothianium Compounds.—Methods used to prepare bicyclic nitrogen compounds are applicable for the preparation of systems that contain sulfur.[93] Bicyclo[1,2,2]thianium-1-heptane chloride and bicyclo-

---

[92] Mills, Parkin, and Ward, *ibid.*, 2613 (1927).

[93] Prelog and Cerkovnikow, *Ann.*, **537**, 214 (1939); Prelog and Kohlbach, *Ber.*, **72**, 672 (1939).

[2,2,2]thianium-1-octane bromide are prepared by the plan shown below.



[a] K_2S, Na + EtOH to form carbinol, 10 per cent HCl or 68 per cent HBr.

Silver oxide converts the salts to the free bases. The thianium heptane chloride is a strong poison, the lethal dose per gram of white mouse being 45γ (a γ is 1/1,000 mg.). The process of second ring closure greatly increases the lethal dose which is $40{,}000\gamma$ for the carbinol. The corresponding values for the thianium octane bromide and the monocyclic carbinol progenitor are 200γ and $20{,}000\gamma$. The ester, ethyl pentamethylenesulfide-4-acetate, is an oil with a very repulsive odor.

Problems

1. Write the structural formulas that are indicated by the following names: 3-Ox-2-azobicyclo[3,3,1]nonane. 2,4-Diazobicyclo[2,2,2]octane. 1,2,3,5,6-Pentazobicyclo[2,1,1]hexane. 6-oxa-1,4-diazobicyclo[3,2,0]heptane. 3-Thiabicyclo[3,1,1]-heptane. 7-Azobicyclo[4,1,0]heptane. Bicyclo[4,2,0]octane. 2-Ox-1-azobicyclo-[2,2,2]octane.

2. What is the product obtained from each of the following reactions? (*a*) Two molecules of chloroacetal with one of sodium sulfide and the product of this reaction allowed to stand with methyl amine and calcium acetonedicarboxylate.[32b] (*b*) Pentamethylene dichloride warmed with benzylamine chlorohydrate.[94] (*c*) Succindialdehyde, methylamine chlorohydrate, and ethyl acetoacetate at pH = 5, temperature of 20 to 22° over a period of 3 days.[31] (*d*) Methyl isoamyl amine shaken with a solution of sodium hypobromide in the cold and the product then heated with concentrated sulfuric acid at 125°.[95] (*e*) 1,6-Diiodohexane heated with piperidine in boiling alcohol.[96]

3. From nonheterocyclic sources and by methods that need not involve reduction except at the last, outline a method of synthesis for the following: (*a*) 1-Phenylethyl-3-carbethoxy-4-piperidyl *p*-aminobenzoate dihydrochloride.[97] (*b*) 2-Methylpiperidine.[98] (*c*) β-Propyl- or β-ethyl-piperidine from trimethylenechlorobromide, $Cl(CH_2)_3Br$.[99] (*d*) N-Phenyl-α-methyl-Δ^2-tetrahydropyridine.[14] (*e*) 2-Propylpyrrolin and 2-propylpyrrolidine.[100] (*f*) 2-Phenyltetrahydropyridine.[101] (*g*) 2-Phenylpiperidine.[102] (*h*) 2,6-Piperidine dicarboxylic acid.[103] (*i*) Ecgonin by an application of Robinson's synthesis.

---

[94] v. Braun, *ibid.*, **37**, 2915 (1904).

[95] Löffler, *ibid.*, **43**, 2044 (1910).

[96] N. Braun, *ibid.*, **43**, 2861 (1910).

[97] Thayer and McElvain, *J. Am. Chem. Soc.*, **49**, 2862 (1927).

[98] Funk, *Ber.*, **26**, 2573 (1893).

[99] Granger, *ibid.*, **28**, 1197 (1895); Günther, *ibid.*, **31**, 2134 (1898).

[100] Gabriel, *ibid.*, **42**, 1259 (1909).

[101] Gabriel, *ibid.*, **41**, 2010 (1908).

[102] Ehrenstein, *ibid.*, **64**, 1137 (1931); *cf.* Ref. 101.

[103] Fischer, *ibid.*, **34**, 2543 (1901).

4. What is the product obtained in each of the following reactions? (*a*) Piperidine treated with benzoyl chloride and the product of that reaction treated with phosphorus pentachloride at 120° (oil-bath temperature).[104] (*b*) γ-Piperidone and benzaldehyde.[20a] (*c*) Amyl nitrite and pseudopelletierine.[105] (*d*) 4-Phenylpyridine dissolved in alcohol and treated with metallic sodium.[106] (*e*) 2-Phenylpiperidine passed over platinized asbestos at 320 to 330°.[102] (*f*) An alcoholic solution of tropinone and piperonal refluxed with a little aqueous potassium hydroxide for 15 min.[30] (*g*) A glacial acetic acid solution of tropinone allowed to react with amyl nitrite under the influence of hydrochloric acid.[67]

5. Suggest a method for the preparation of the following: (*a*) 1-Methyl-azocyclodecane, $CH_3N(CH_2)_9$, from 1-azobicyclo[5,3,0]-decane.[86] (*b*) Pyridine-2,3-dicarboxylic acid from lupinane.[107] (*c*) Quinuclidine 2-carboxylic acid from γ-pyrone.[28] (*d*) 1-Azobicyclo[3,2,1]octane from a piperidine compound.[108]

6. When the hydrochloride of ecgonine is refluxed with phosphorus oxychloride, anhydroecgonine is obtained as the hydrochloride $C_9H_{13}NO_2{\cdot}HCl$. The anhydroecgonine is then treated with bromine (addition to double bond) while in acetic acid as a solvent, and the perbromide that results is heated in alcohol or acetic acid to produce the hydrobromide of anhydroecgonine dibromide, $C_5H_7N(CH_3)CH(Br)$-$CH(Br)CO_2H{\cdot}HBr$. This product is dissolved in water and treated at 60° with sodium carbonate. When evolution of carbon dioxide has ceased, the mixture is rapidly steam distilled. Methyl amine and dihydrobenzaldehyde, C_6H_7CHO, are collected in the distillate. Explain the occurrence of this aldehyde product, which at one time caused considerable confusion with respect to the structure of tropine and suggested the presence of a six-membered carbon ring.[109]

7. Tropine and ψ-tropine are isomeric alcohols which by oxidation give the same compound, tropinone. Account for the difference between the two compounds.[110]

8. What is the final product[111] obtained by treatment of ethyl methylacetoacetate with the following sequence of reagents? (*a*) γ-Bromopropyl ethyl ether (how prepared?) in dioxane solution in presence of sodium ethoxide. (*b*) Strong sodium hydroxide at 250° under 1,000 lb. of nitrogen for 8 hours. (*c*) Hydrobromic acid. (*d*) Alcoholic ammonia at room temperature for 48 hr. (*e*) Palladium on asbestos at 270 to 280°. (*f*) Butyllithium followed by formaldehyde. The product has the formula $C_{14}H_{14}N_4O_8$.

9. Name the products obtained from acetaldehyde by means of the following reagents and conditions employed in a sequence of reactions that lead to a product with the composition $C_6H_{14}NCl$:[112] (*a*) Dilute alkali. (*b*) Aluminum amalgam. (*c*) Fuming hydrobromic acid at 100° in a closed tube. (*d*) Potassium cyanide in an alcoholic-aqueous solution. (*e*) An excess of metallic sodium in alcohol. (*f*) Hydrochloric acid until neutral, and the dried salt heated with lime and the distillate neutralized with hydrochloric acid.

10. Describe methods for preparing the following compounds chiefly from available pyridine derivatives: (*a*) γ-α-(2-phenylethyl)-piperidinopropylbenzoate.[72] (*b*)

---

[104] v. BRAUN, *ibid.*, **37**, 2915 (1904).

[105] CIAMICIAN and SILBER, *Gazz. chim. ital.*, **29**, i, 408 (1899).

[106] BALLY, *Ber.*, **20**, 2590 (1887).

[107] KING, *Ann. Repts*, **30**, 231 (1934); *cf.* Ref. 36.

[108] PRELOG, HEINBACH, and CERKOVNIKOW, *J. Chem. Soc.*, 677 (1939).

[109] EICHENGRÜN and EINHORN, *Ber.*, **23**, 2870 (1890); *cf.* Ref. 68.

[110] WILLSTÄTTER and IGLAUER, *Ber.*, **33**, 1170 (1900).

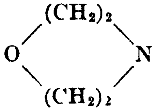
[111] FINKELSTEIN and ELDERFIELD, *J. Org. Chem.*, **4**, 365 (1939).

[112] FRANKE and KOHN, *Monatsh.*, **23**, 877 (1902).

Methyl piperidine-2-acetate-1-β-propionate and its conversion to a bicyclic compound.[85] (*c*) 1-Azobicyclo[2,2,1]heptane.[113] (*d*) γ-(2-piperidyl)-propyl alcohol.[26] (*e*) 2-Ethylquinuclidine.[88] (*f*) β-Vinylpiperidine (from nicotinic acid).[114] (*g*) α-Vinylpiperidine.[115] (*h*) β-Vinylpiperidine.[116] (*i*) γ-Piperidylethanol and its conversion to quinuclidine.[23] (*j*) 2-(β-hydroxy)-piperdine.[74] (*k*) Tropinepinacone, $C_{16}H_{28}N_2O_2$.[117] (*l*) Lobelan, $C_{21}H_{27}N$, which is the methyl-free parent compound of the lobelia alkaloids.[80]

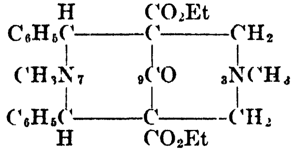
11. Suggest a method for preparing *d,l*-4-phenyl-4′-carbethoxybispiperidinium-1,1′-spiran bromide.[118]

12. What is the product of the reaction of piperidine with 33 per cent aqueous formaldehyde in the presence of potassium carbonate? The product of this reaction, with hydrogen sulfide, gives $C_6H_{13}NS$ and $C_{12}H_{24}N_2S$, depending on the comparative severity of the conditions. What is the structure and name of the two final products?

Would morpholine,  undergo the same reactions?[119]

13. Devise a sequence of steps for synthesizing diethyl 3,7-dimethyl-6,8-diphenyl-9-oxobispidine-1,5-dicarbboxylate.[120]

(The bispidine ring is the piperidine ring taken twice as indicated.)



How would the compound be named according to the system used for bicyclic compounds?

14. Outline a sequence of steps that should convert pseudopelleterine to cyclooctatetrene.[121]

15. Show a sequence of steps by which the following compounds can be prepared from a piperidine compound: (*a*) 5-Aminocaprylaldehyde.[122] (*b*) Inactive lysine, $H_2N(CH_2)_4CH(NH_2)COOH$.[123] (*c*) 1,5-Dichlorooctane.[124] (*d*) Suberic acid (from ψ-pelletierine).[125]

16. Name the products[126] obtained in each step of the following sequence of reactions that begins with ethyl nicotinate hydrochloride and ends with $C_8H_{15}N$: (*a*)

[113] Clemo and Prelog, *J. Chem. Soc.*, 400 (1938).

[114] Merchant and Marvel, *J. Am. Chem. Soc.*, **50,** 1197 (1928).

[115] Ladenburg, *Ber.*, **22,** 2587 (1889); Einhorn, *Ann*, **265,** 229 (1891).

[116] Iddles, Lang, and Gregg, *J. Am. Chem. Soc.*, **59,** 1945 (1937).

[117] Willstätter, *Ber.*, **31,** 1672 (1898).

[118] Mills and Bain, *J. Chem. Soc.*, **127,** 2507 (1925).

[119] Binz and Pence, *J. Am. Chem. Soc.*, **61,** 3134 (1939).

[120] Mannich and Mohs, *Ber.*, **63,** 608 (1930); Mannich and Veit, *ibid.*, **68,** 506 (1935).

[121] Willstätter and Wane, *ibid.*, **44,** 3423 (1911).

[122] Wolffenstein, *ibid.*, **28,** 1459 (1895).

[123] v. Braun, *ibid.*, **42,** 839 (1909).

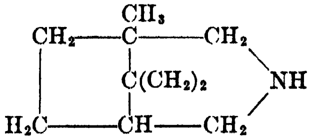
[124] v. Braun and Schmitz, *ibid.*, **39,** 4365 (1906).

[125] Ciamician and Silber, *Gazz. chim. ital.*, **29,** ii, 104 (1899).

[126] Prelog, Heimbach, and Seiwerth, *Ber.*, **72,** 1319 (1939).

Ethyl acetate and sodium ethoxide. (*b*) Catalytic hydrogen over platinum oxide at low pressure. (*c*) Sodium and alcohol. (*d*) Sixty-seven per cent hydrobromic acid at 100°. (*e*) Sodium hydroxide at 50°.

17. Camphidine (how prepared?)



is treated with benzoyl chloride and the product caused to react with phosphorus pentachloride. What compound is produced?[127]

18. The hygrines are a mixture of alkaloids obtained from Peruvian coca leaves. One of these alkaloids, hygrine, $C_8H_{15}ON$, yields hygrinic acid, $C_6H_{11}O_2N$ when oxidized with chromic acid; and this acid in turn loses carbon dioxide when heated or treated with strong sulfuric acid and thus changes to N-methylpyrrolidine. What do these facts suggest as to the formula for hygrinic acid? Suggest a method for synthesis from a nonheterocyclic source.[128]

19. The formula for hygrine is the same as that of hygrinic acid except that an acetonyl group is in the position of the carboxyl. Suggest a method for synthesis of this compound from a pyrrole derivative.[129]

20. *d,l*-Lelobanidin, $C_{18}H_{29}O_2N$, an accessory alkaloid of the lobelia group, is oxidized to *d,l*-lelobanine, $C_{18}H_{25}O_2N$, a diketo base. This compound in turn undergoes a Hofmann degradation (MeI, Ag_2O) which produces dimethylamine and a doubly unsaturated diketone, $C_{17}H_{20}O_2$. Catalytic hydrogenation converts this compound to a saturated glycol, $C_{17}H_{28}O_2$, which in turn is oxidized by chromic oxide to the saturated diketone, $C_{17}H_{24}O_2$. This compound is suspected of being 1-benzoyl-7-propionyl-*n*-heptane. Suggest a synthesis. What is the probable structure of the original heterocyclic compound? What other reactions would probably be tried in order to help determine the structure?[130]

21. Oxidation of nicotine usually results in cleavage of the pyrrolidine ring. Suggest a series of steps that might effect oxidation of the pyridine but preserve the pyrrolidine ring.[131]

---

[127] v. Braun, *ibid.*, **42**, 1429 (1909).

[128] Willstätter, *ibid.*, **33**, 1160 (1900); *Ann.*, **326**, 91 (1903).

[129] Hess, *Ber.*, **46**, 3113, 4104 (1913).

[130] Wieland, Koschara, Dane, Renz, Schwarze, and Linde, *Ann.*, **540**, 103 (1939).

[131] Karrer and Widmer, *Helv. Chim. Acta*, **8**, 364 (1925).

CHAPTER X

THE QUINOLINE COMPOUNDS

The condensed benzopyridine system, named as the quinoline type from its relation to the quina alkaloids, is one that has been studied extensively because of the valuable pharmaceutical properties of many compounds in the series. Besides its occurrence in alkaloids, the quinoline nucleus is found also in coal tar and certain petroleum bases. Many valuable synthetic dyes and medicinals have been produced also from derivatives in the series. The methods of preparation of the heterocyclic ring differ considerably from those in the pyridine series, but the reactions that the heterocyclic ring undergoes are very similar.

Methods of Synthesis.—Since the preparations of quinoline must proceed from available materials, the different methods will be classified according to the principal types of compounds employed. These groups include (*a*) primary aromatic amines with no *o*-substituent, (*b*) aromatic amines with an *o*-substituent, (*c*) five-membered rings capable of ring enlargement, and (*d*) saturated isocyclic systems that undergo ring closure similar to that found in the preparation of pyridine compounds.

From Aromatic Amines with No o-Substituent.—*Skraup's synthesis*[1] is one of the most common methods for the preparation of quinoline compounds. The account of his work is a classic, because it is such a beautiful example of the value of balancing chemical equations and of making appropriate deductions. The initial suggestion was derived from the work of Graebe,[2] published a year earlier, in which the product of the action of zinc dust on alizarin blue, $C_{17}H_{10}O_4N$, itself prepared from β-nitroalizarin and glycerol in the presence of sulfuric acid, was considered to be an anthraquinoline, $C_{17}H_{11}N$. Skraup, accordingly, tried the reaction of nitrobenzene with glycerol in the presence of sulfuric acid and obtained a small amount of quinoline. He then tried the reaction of aniline with glycerol under the same conditions and again found a small amount of quinoline. He observed, however, that one equation required oxygen for a balance and the other needed hydrogen.

$$C_6H_5NO_2 + C_3H_8O_3 = C_9H_7N + 3H_2O + O_2$$
$$C_6H_5NH_2 + C_3H_8O_3 = C_9H_7N + 3H_2O + H_2$$

---

[1] SKRAUP, *Monatsh.*, **1**, 316 (1880); **2**, 139 (1881).

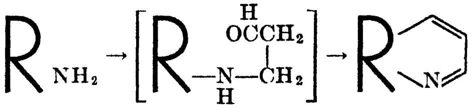
[2] GRAEBE, *Ann.*, **201**, 333 (1880).

He, therefore combined the two preparations and used just enough aniline and nitrobenzene to convert all the hydrogen to water as given below. The yield rose from a trace or small amount to 60 per cent.

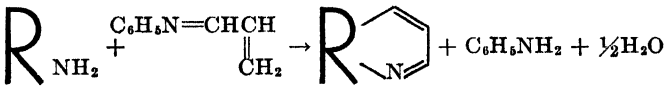
$$2C_6H_5NH_2 + C_6H_5NO_2 + 3C_3H_8O_3 = 3C_9H_7N + 11H_2O$$

The principle of this reaction remains the same today. Nitrobenzene is still a convenient oxidizing agent,[3] but arsenic acid may also be used. Copper sulfate or ferrous sulfate serve as catalysts. Acetic or boric acid facilitates the process in some cases. The reaction is vigorous and sometimes difficult to control.

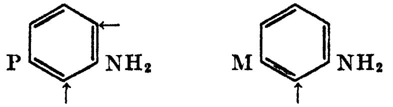
The reaction proceeds by way of the intermediate formation of acrolein and, for all practical purposes, is as if the amino group adds across the double bond.



Amine and aldehydes, however, form Schiff bases readily. Hence the true course of this reaction may be by intermediate formation of an anil[4] and the reaction of the anil with a second molecule of aniline.



In any event, the products obtained with homologues of acrolein are as if the amine adds to an olefin and ring closure completes the process. The position at which the ring forms[5] is unaffected by substituents in the ortho or para position of the benzene ring. A substituent (see below) in the meta position, however, directs ring closure (*a*) to either side of the amino group or (*b*) to the vicinal position, depending on whether the group is ortho- and para-directing (P) or meta-directing (M).



(Arrow points to the position at which ring closure occurs)

This elegant synthesis has suggested the development of other closely related preparations. For example, substitution of glycol for glycerol causes the formation of quinaldine. *Döbner and Miller*[6] made the reasonable interpretation that the glycol changed to acetaldehyde. They, therefore, developed the synthesis with two molecules of acetaldehyde, now known by their name. An aldehyde and a ketone combination with aniline is known as *Beyer's*[7] *method*, and 2 molecules of a ketone with aniline is called *Riehm's*[8] *synthesis*. Pyruvic acid may replace one of the aldehydes in the Döbner and Miller synthesis, whereupon the reaction becomes *Döbner's pyruvic acid synthesis.*[9] Other quinoline carboxylic acids can be made by other modifications.[10]

---

[3] Clarke and Davis, *Org. Synthesis, Coll. Vol.* I, 2d ed., 478 (1941).

[4] Blaise and Maire, *Bull. soc. chim.* [4], **3**, 662, 664 (1908).

[5] Manske, *Chem. Rev.*, **30**, 113 (1942).

[6] Döbner and Miller, *Ber.*, **14**, 2812 (1881); **16**, 1664, 2465 (1883); **17**, 1698, 1712 (1884).

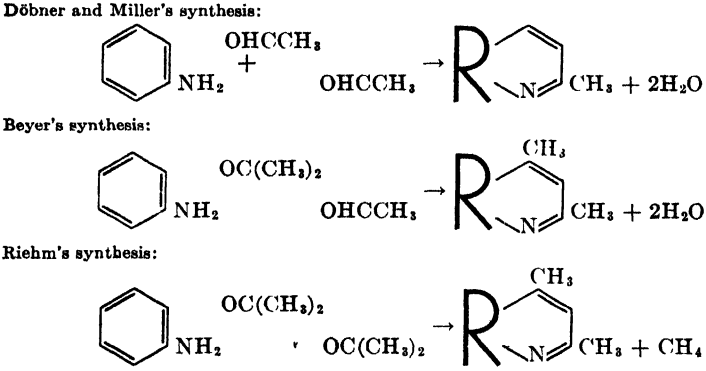


FIG. 1.—Synthesis of quinoline compounds by reaction of aniline with (1) 2 molecules of an aldehyde, (2) one aldehyde and a ketone, and (3) 2 molecules of a ketone. Intermediate α,β-unsaturated aldehydes or ketones probably form in each process.

These reactions and others are listed below in such a way as to show their common character. A conjugated carbonyl-olefin system

Reagents, that react with anilines, arranged in the order in which the atoms become parts of the ring	Quinoline products with substituents in position			Name of reaction
	α	β	γ	
$—C_1—————C_2{=}C_3—$				
$CH_2{=\!=}HC—CHO$	....	......	......	Skraup
CH_3CHO CH_3CHO	CH_3	......	......	Döbner and Miller
CH_3CHO $CH_3C(O)CH_3$	CH_3	......	CH_3	Beyer
$(CH_3)_2CO$ $CH_3C(O)CH_3$	CH_3	......	CH_3	Riehm
CH_3CHO $CH_3C(O)CO_2H$	CH_3	......	CO_2H	Döbner's pyruvic acid
CH_3CHO $EtO_2CCH_2C(O)CO_2Et$	CH_3	CO_2Et	CO_2Et	Simon and Conduchó
$HO_2CCH{=\!=}CHC(O)C_6H_5$	CH_3	......	C_6H_5	

---

[7] BEYER, *J. prakt. Chem.*, **33**, 393 (1886); *Ber.*, **20**, 1767 (1887).

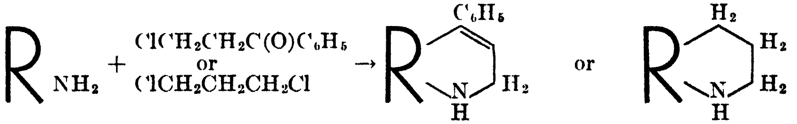
[8] ENGLER and RIEHM, *ibid.*, **18**, 2245 (1895); RIEHM, *Ann.*, **2389** (1887); LEVIN and RIEHM, *Ber.*, **19**, 1394 (1886).

[9] DÖBNER, *ibid.*, **20**, 277 (1887).

[10] SIMON and CONDUCHÉ, *Compt. rend.*, **139**, 297 (1904).

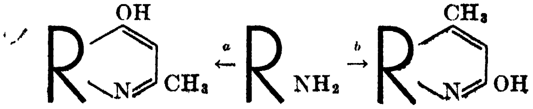
forms from the condensation of an active carbonyl with an appropriate active methyl or methylene group. The aniline then adds across the double bond of the olefin to produce a β-phenylaminopropionaldehyde or propiophenone, ring closure takes place, oxidation eliminates the extra hydrogen atoms. The conjugated pyridine system tends to form, even if it becomes necessary to cleave a carbon-carbon bond as in the case of Riehm's synthesis where methane is lost. Innumerable combinations are possible. Carboxyl or carbethoxy groups may be used in place of hydrogen in order to get the activation of hydrogen atoms or carbonyl group necessary for the formation of a conjugated carbonyl-olefin system, since such groups can be eliminated readily at the end of the synthesis.

A β-phenylaminopropiophenone can be prepared also from aniline and a β-chloropropiophenone.[11] The reaction of aniline with 1,3-dichloroalkane[12] is closely related. The dihydro- and tetrahydro-quinoline products formed, respectively, can be readily converted to quinolines by mild oxidation.



In general, the addition of ammonia and amines to the olefinic system of the enol form of ethyl acetoacetate, followed by elimination of water, gives an ester of β-aminocrotonic acid. It is not surprising, therefore, that aniline and ethyl acetoacetate condense similarly in the cold to form ethyl β-phenylaminocrotonate. This compound is somewhat similar to the β-phenylaminopropionaldehydes and β-propiophenones already discussed. Hot sulfuric acid or boiling hydrochloric acid closes the ring. 2-Methyl-4-carbostyril results.[13]

On the other hand, when ethyl acetoacetate is heated with aniline, the conventional formation of an anilide occurs. Cold concentrated sulfuric acid closes the ring. 4-Methyl-2-carbostyril results.[14] This process is sometimes called Knorr's quinoline synthesis.



[a] Cold $CH_3C(O)CH_2CO_2Et$, hot H_2SO_4 or boiling HCl.
[b] $CH_3C(O)CH_2CO_2Et$ at 110°, cold conc. H_2SO_4.

---

[11] Heon-Feu, *Bull. soc. chim.* [5], **2**, 90 (1935).

[12] Rindfusz and Harnack, *J. Am. Chem. Soc.*, **42**, 1720 (1920).

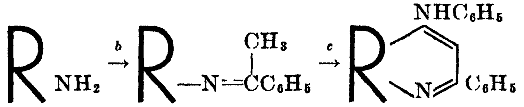
[13] Conrad and Limpack, *Ber.*, **20**, 944 (1887); **21**, 523 (1888); **24**, 2990 (1891).

[14] Knorr, *Ann.*, **236**, 70 (1886); Ewins and King, *J. Chem. Soc.*, **103**, 104 (1913).

The monoanilide of a malonic acid yields a 2,4-dihydroxy quinoline with phosphorus pentachloride.[15] Ethyl benzoylacetate and aniline give only 4-hydroxy-2-phenylquinoline,[16] whether in hot or cold sulfuric acid.

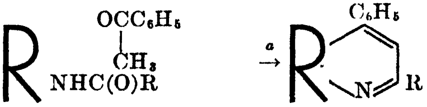
The preparation of quinoline compounds often appears complex, when in reality the changes are conventional. For example, diphenylthiourea condenses with acetophenone to form 2-phenyl-4-anilinoquinoline.[17] The urea first decomposes to aniline and phenylisothiocyanate. The products then combine with acetophenone according to the standard pattern, save for the fact that the final reagent is an α,β-unsaturated thioanilide and not an ester. A 4-anilino instead of a 4-hydroxy product results.

$$C_6H_5NHC(S)NHC_6H_5 \xrightarrow{a} C_6H_5NH_2 + C_6H_5NCS$$



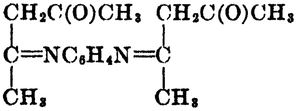
^{a} Heat. ^{b} $CH_3C(O)C_6H_5$. ^{c} C_6H_5NCS causes the intermediate formation of $RNHC(C_6H_5)=CHC(S)NHC_6H_5$ which, in turn, condenses to the quinoline compound.

The reaction of an acid anilide[18] with an acetophenone under the dehydrating influence of zinc chloride appears to be essentially the same as those which start with an unsubstituted aniline.

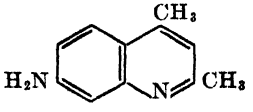


^{a} $ZnCl_2$ at 250 to 300° for 4 days.

The reactions described are general for all anilines, although irregularities are occasionally noted. For example, p-phenylenediamine[19] reacts with 2 molecules of acetylacetone to form the expected dianil intermediate, but undergoes no further change to a quinoline compound.



From p-phenylenediamine



From m-phenylenediamine

The m-isomer forms the initial product of the same empirical composition but undergoes ring closure on one side only to give 7-amino-2,4-dimethylquinoline. Formanilide[20] does not behave as does acetanilide, but appears to undergo a rearrangement of its formyl group to give *o*-aminobenzaldehyde, which condenses with acetophenone according to the general scheme outlined in the next section.

---

[15] RUGHEIMER, *Ber.*, **17**, 736 (1884); **18**, 2975 (1885).

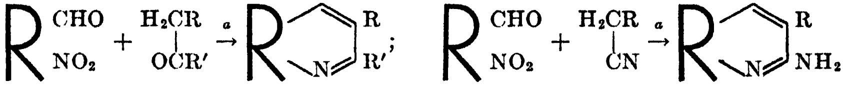
[16] KNORR, *Ann.*, **245**, 378 (1888).

[17] DZIEWONSKI and MOSZEW, *Roczniki Chem.*, **12**, 482, 925 (1932); *C.A.*, **27**, 3937 (1933); **28**, 152 (1934).

[18] SPALLINO and SALIMERI, *Gazz. chim. ital.*, **42**, 607 (1912).

[19] MARCHWALD and SCHMIDT, *Ann.*, **274**, 367 (1893).

Synthesis from o-Substituted Anilines.—The preparation of quinolines from *o*-substituted anilines or from compounds capable of forming anilines in the course of reaction is very common. In the two general illustrations shown below, the chain is first lengthened by condensation between the aldehyde and the active methylene group, and the ring is then closed by reduction. There are innumerable variants of this scheme. If an appropriate ketone, or an acid such as anthranilic, is used in place of *o*-nitrobenzaldehyde, a substituent is introduced in the gamma position.

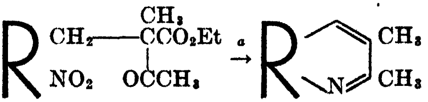


R = alkyl, aryl, carbethoxy, cyano group. R′ = alkyl or aryl group.
[a] Condensation with reduction.

If benzyl chlorides are used in place of the benzaldehyde, dihydroquinolines may form.

o-Nitrobenzaldehyde and acetone obviously give α-methylquinoline,[21] and *o*-nitrobenzylchloride with acetone gives the corresponding dihydro compounds.[22] If ethyl methyl ketone[23] is used in place of acetone in the reaction with *o*-nitrobenzaldehyde, the product is 2,3-dimethylquinoline. This tendency for the ethyl side of the ketone to be more reactive than the methyl side in this condensation parallels the experience in the Fischer indole synthesis where 2,3-dimethylindole rather than 2-ethylindole resulted from the use of ethyl methyl ketone. (Compare this effect with that discussed in part 2 of the quinine synthesis, page 290.)

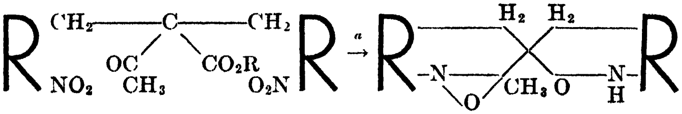
If ethyl acetoacetate is used in place of acetone, a carbethoxy-substituted quinoline results. Ethyl acetoacetate can sometimes be used in special ways. For instance, an alkyl-substituted ethyl acetoacetate condenses with *o*-nitrobenzyl chloride. If phosphorus and hydriodic acid are then used as the reducing agent, simultaneous hydrolysis, decarboxylation, and ring closure take place. 2,3-Dimethylquinoline forms



[a] P + HI.

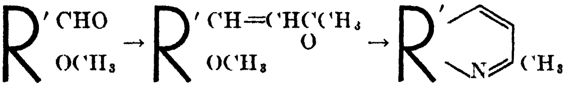
[20] Pictet and Barbier, *Bull. soc. chim.*, 111, **13**, 26 (1895).
[21] Drewson, *Ber.*, **16**, 1953 (1883).
[22] Jackson, *ibid.*, **14**, 889 (1881).
[23] Heller, Lauth, and Buchwalt, *ibid.*, **55**, 483 (1922).

without any dihydro product.[24] If the ethyl acetoacetate portion contains an *o*-nitrobenzyl group and stannous chloride is used as the reducing agent, a double ring closure takes place. A spiran forms.[25]



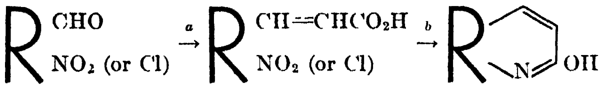
[a] $SnCl_2$ in HCl-HOAc solution.

Quinolines can form without an *o*-nitro group. In the example below, a methoxy group present in the starting reagent is replaced by an amino group when heated with alcoholic ammonia. Ring closure simultaneously occurs.[26]



R′ = $-C_6H_3NO_2$ with the NO_2 ortho to the oxygen or nitrogen atom.

The Perkin condensation can be used to prepare intermediates that have a carboxyl group so situated that an α-hydroxyquinoline, *i. e.*, [27-30]



Perkin condensation.

[a] $Ac_2O + NaOAc$. [b] If NO_2 is used in the above formula the reagents are NH_4SH,[27] $FeSO_4 + BaSO_4$[28] or Sn + HCl[29] followed by heat. If Cl is used in the above formula the reagents are NH_3 + Cu at 125 to 130°[30] followed by heat.

a carbostyril, forms when the ring closes. Similarly, the Claisen condensation[31] of ethyl anthranilate or the reaction of an *o*-nitrobenzoyl chloride[32,33] with ethyl malonate leads (see next page) to 2,4-dihydroxyquinoline. Since hydroxy groups on heterocyclic rings are converted to chloro groups by phosphorus oxy- and penta-chlorides and thence by reduction are eliminated, a wide range of possibilities is present.

[24] Jaenisch, *ibid.*, **56**, 2450 (1923).

[25] Gabriel and Wolter, *Ber.*, **56**, 2445 (1923).

[26] v. Miller and Kinkelin, *ibid.*, **22**, 1716 (1889).

[27] Chiozza, *Ann.*, **83**, 117 (1854); Friedländer and Ostermaier, *Ber.*, **14**, 1916 (1881); *ibid.*, **47**, 3669 (1914).

[28] Tiemann and Oppermann, *ibid.*, **13**, 2070 (1880).

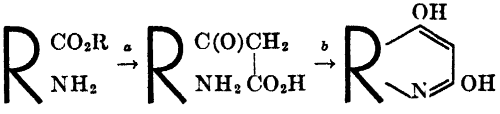
[29] Morgan, *Chem. News*, **36**, 269 (1877); Friedländer and Weinberg, *Ber.*, **15**, 321, 1421, 2103 (1882).

[30] Meyer and Beer, *Monatsh.*, **34**, 1173 (1913).

[31] Erdmann, *Ber.*, **32**, 3570 (1899).

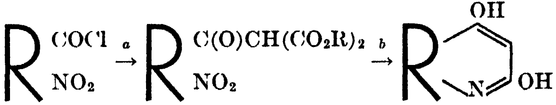
[32] Bischoff, *Ann.*, **251**, 360, 366, 376 (1889).

[33] Gabriel, *Ber.*, **51**, 1500 (1918).



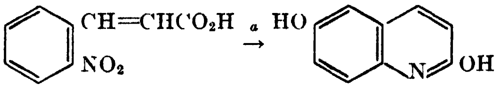
Claisen condensation.

[a] CH_3CO_2Et + Na,[31] HX + H_2O. [b] Heat.



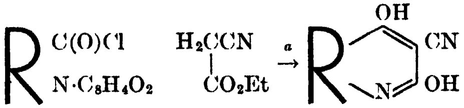
[a] $H_2C(CO_2R)_2$ + NaOEt.[32] [b] Sn + HCl or HI + P. A small amount of 2-ethoxy-3-carbethoxyquinoline is obtained if Zn + HCl is used.

Many other variations can be introduced in these processes. If the reduction of the *o*-nitrocinnamic acid is carried out electrolytically, the intermediate hydroxylamine undergoes a rearrangement. Subsequent ring closure gives 6-hydroxycarbostyril.



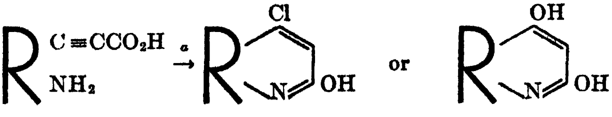
[a] Ring closure at 160° of the reduced product.

o-Aminobenzoyl chloride, from anthranilic acid, may require protection of its amino group. The example[34] below shows the phthalimido group as the protecting agent, to prevent addition of the amino group to the nitrile.



[a] NaOH, warm CH_3CO_2H.

Reduction of *o*-nitrophenylpropiolic acid, *o*-$NO_2C_6H_4C{\equiv}CCOOH$, with zinc and hydrochloric acid causes hydroxylation of the triple bond so that ring closure gives 2,4-dihydroxyquinoline.[35] *o*-Aminophenylpropiolic acid, treated with hydrochloric acid yields 4-chlorocarbostyril[36] by ring closure and simultaneous addition of halogen acid to the triple bond; when treated with sulfuric acid, it yields 2,4-dihydroxyquinoline[36] by ring closure and simultaneous hydroxylation of the bond.



[a] HCl or H_2SO_4, respectively.

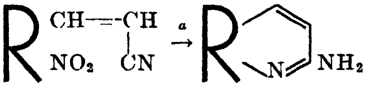
---

[34] Gattermann, *ibid.*, **27,** 1936 (1894).

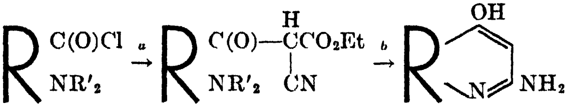
[35] Heller and Tischner, *ibid.*, **42,** 4555 (1909); *ibid.*, **34,** 2716 (1901).

[36] Baeyer and Bloem, *ibid.*, **15,** 2147 (1882).

If a nitrile is used in place of a carbethoxy group in the first phase of these reactions, ring closure takes place by addition of the amine to the nitrile group. An α-aminoquinoline results. Two examples[37,38] are given below.

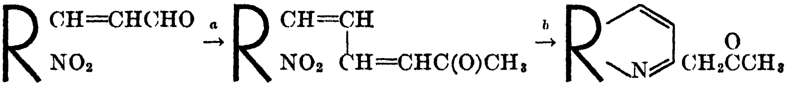


[a] Sn + HCl, NaOR and heat.



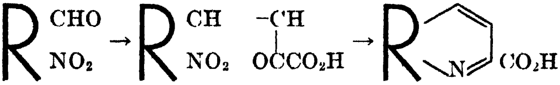
[a] Reaction with $CNCH_2CO_2Et$.[37] [b] HI + P.[38] R'_2 = phthalyl radical, $C_6H_4(CO)_2$.

A similar addition across a carbon-carbon double bond gives an α-acetonylquinoline compound.[39]

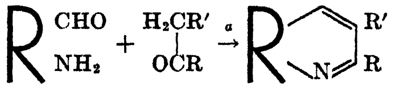


[a] $CH_3C(O)CH_3$. [b] Concentrated alcoholic solution of stannous chloride.

When o-nitrobenzaldehyde is condensed with pyruvic acid, the intermediate thus produced gives an α-quinoline carboxylic acid by ring closure.



The reaction of anthranilaldehyde (o-aminobenzaldehyde) with compounds that contain an active methylene group, adjacent to an aldehyde, ketone, or acid group is of the same general type under discussion in this section, but has been studied so extensively that it is called the *Friedländer synthesis*.[40] Anthranilaldehyde[41] is readily obtained by reduction of 2-nitrobenzaldehyde with ferrous sulfate and ammonia at 90 to 100°.



R = H, CH_3, C_6H_5, OH, CH=NOH, —C_4H_4N, and others. R′ = H, CH_3, C_2H_5, C_6H_5, OH, $COCH_3$, COOEt, NH_2, and others.

[a] Piperidine or sodium hydroxide.

---

[37] Gabriel, *ibid.*, **51,** 1500 (1918).

[38] Pschorr, *ibid.*, **31,** 1289 (1898).

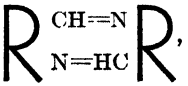
[39] Fischer and Kuzel, *ibid.*, **16,** 163 (1883).

[40] Friedländer, *ibid.*, **15,** 2572 (1882).

[41] Bamberger, *ibid.*, **60,** 314 (1927).

Other amino aldehydes may be employed. 5-Nitro-2-aminobenzaldehyde,[42] for example, is obtained by nitration of the acetyl derivative of *o*-aminobenzaldehyde. 6-Aminopiperonal[43] or aminoveratraldehyde[43] is prepared by nitration of piperonal or veratraldehyde, condensation of the product with *p*-toluidine in order to protect the aldehyde group, reduction of the nitro group with sodium sulfide, and recovery of the aldehyde by hydrolysis with dilute acid. Acetaldehyde, acetone, ethyl acetoacetate, succinic anhydride, and many other compounds serve as the second component in the Friedländer synthesis. Some examples are in the table below. The synthesis of quinaldine (*A*) shows the effect that concentration of hydrogen ions has on the course of reaction. At pH = 12, the yield is only 11 per cent. At pH = 3, the product is anhydro-*o*-aminobenzaldehyde,

	Portion of reagent that			Condition for reaction with *o*-amino-benzaldehyde	Quinoline derivative
	Serves as an α-substituent	Forms part of ring	Serves as a β-constituent		
A	CH_3—	$C(O)CH_3$		7 days at pH = 13	2 methyl-
B	CH_3—	$C(O)CH_2$—	CO_2Et	8 days at pH = 8	2 methyl-3-carbethoxy-
C	EtO_2C—	$C(O)CH_2$—	CO_2Et	KOH 1 week	2,3-dicarbethoxy-
D	CH_3—	$C(O)CH_2$—	$C(O)CH_3$	Trace of piperidine	2-methyl-3-acetyl-



$$R\begin{matrix}CH{=}N\\N{=}HC\end{matrix}R,$$

in 80 per cent yield. At pH = 5, the yield of this by-product is 25 per cent. At pH of 7 to 10, no quinaldine is formed even after 7 weeks. These reactions at specific concentrations at room temperature simulate processes that can occur in nature and are therefore known as *biogenic syntheses*.[44] A similar specific effect is noted in the reaction with ethyl acetoacetate (*B*) which gives in 8 days at 25° a 66 per cent yield at pH = 9, but 17 and 43 per cent yields at pH = 7 and 11, respectively. Ethyl oxaloacetate (*C*) yields the ester of a dicarboxylic acid.[45] Acetylacetone (*D*) forms

---

[42] Cohn and Springer, *Monatsh.*, **24**, 87 (1903).

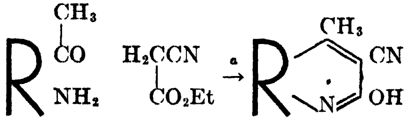
[43] Rilliet and Kreitmann, *Helv. Chim. Acta*, **4**, 588 (1921); Rilliet, *ibid.*, **5**, 547 (1922).

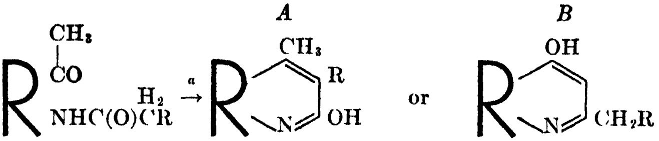
[44] Schöpf, *Ann.*, **497**, 1 (1932); Schöpf and Lehmann, *ibid.*, **497**, 7 (1932).

[45] Koller and Strang, *Monatsh.*, **50**, 48 (1928).

3-acetylquinaldine;[46] benzoylacetone gives the corresponding benzoyl compound.[47]

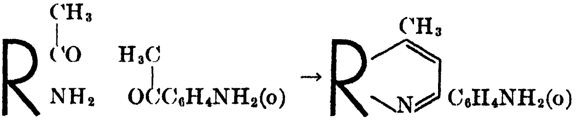
o-Aminoacetophenone[48] can be used in place of the anthranilaldehyde. This reaction proceeds better if the acyl derivative[49] is used. The aminoacetophenone has, however, an active methyl group as well as a





ª Heated in alcoholic caustic solution.

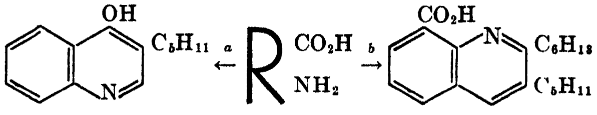
carbonyl group. Hence the intramolecular condensation of an acylated *o*-aminoacetophenone, which might lead to (*A*) as in the example seen above, may join instead at a different methylene-carbonyl pair and form the 4-hydroxyquinoline shown in (*B*). As R is made more negative by C_6H_5, CN, COOEt, $COOCH_3$, COC_6H_5 groups, the adjacent methylene group becomes more reactive and the principal reaction proceeds toward the 2-hydroxyquinoline.[50] As a further complication, two aminoacetophenones may sometimes condense together as shown below.



Anthranilic acid is also used in a similar way because of its availability. This process is sometimes called *von Niementowski's*[51] *method.* The reaction proceeds with more difficulty than in the case of the aldehyde, as might be expected from the relative activity of aldehydes and acids in condensations. Hence other products have a chance to form. For example, the reaction with oenanthaldehyde goes in two directions: part toward the expected 3-amyl-4-hydroxyquinoline and a very much

---

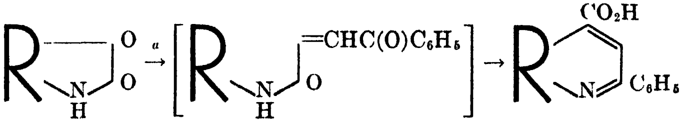
[46] Stark, *Ber.*, **40**, 3425 (1907).
[47] Stark and Hoffmann, *ibid.*, **42**, 715 (1909).
[48] Guareschi, *ibid.*, **26**, R944 (1893).
[49] Camps, *ibid.*, **32**, 3228 (1899)..
[50] Camps, *Arch. Pharm.*, **240**, 135 (1902).
[51] v. Niementowski, *Ber.*, **27**, 1394 (1894).



[a] Condensation with 1 molecule of $C_6H_{11}CH_2CHO$.
[b] Condensation with 2 molecules of $C_6H_{11}CH_2CHO$.

larger part toward a 2,3-dialkylquinoline-8-carboxylic acid by a Döbner and Miller synthesis. In fact, acetaldehyde,[52] propionaldehyde, and chloral go exclusively by the latter path or form Schiff bases. Ethyl acetoacetate[53] likewise reacts in one or two ways but can be confined to one path if the ortho position is blocked, say by a methoxy group.

Synthesis from Other Ring Systems.—The third general method consists of deriving quinolines from other ring compounds either by expanding a five- to a six-membered ring or by degrading an aromatic ring. One illustration in this class is the well-known *Pfitzinger*[54] *reaction* by which alkali causes isatin to condense with ketones or acids that have a reactive methylene group. This reaction is sometimes regarded as



[a] $CH_3C(O)C_2H_5$ + NaOH.

essentially the same as the Friedländer synthesis since the isatin system opens to an *o*-aminoketo acid, which can condense as would *o*-aminobenzaldehyde. Hydriodic acid will sometimes effect the Pfitzinger reaction also.[55]

Isatin will also expand to 2,3-dihydroxyquinoline when treated with diazomethane. This reaction is general for enlarging cyclic ketones[56] (see pages 342, 372).

Nonoxygenated indoles can also be converted to quinolines. Chloroform and sodium alkoxide convert indoles to β-chloroquinoline[57] in the same way that pyrroles sometimes change to β-chloropyridine. 2-Methylindoles change to N-methyl-3-methyl-1,2-dihydroquinolines[58] when heated with methyl iodide at 100°. A dull red heat causes alkylated

[52] v. Niementowski and Orzechowski, *ibid.*, **28**, 2809 (1895).

[53] Froelicher and Cohen, *J. Chem. Soc.*, **119**, 1425 (1921).

[54] Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897).

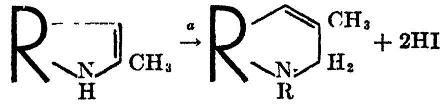
[55] Lindwall and Maclennon, *J. Am. Chem. Soc.*, **54**, 4739 (1932); DuPuis and Lindwall, *ibid.*, **56**, 471 (1934).

[56] Heller, *ibid.*, **51**, 424 (1918); **52**, 741 (1919).

[57] Magnanini, *ibid.*, **20**, 2608 (1887); **21**, 1940 (1888).

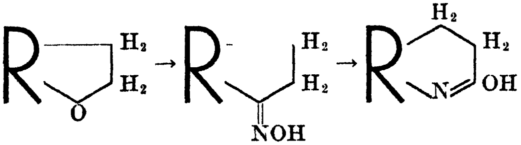
[58] Fischer and Steche, *Ann.*, **242**, 348 (1887).

indoles to change to quinoline, *e.g.*, N- or 2-methylindole[59] rearranges to quinoline.



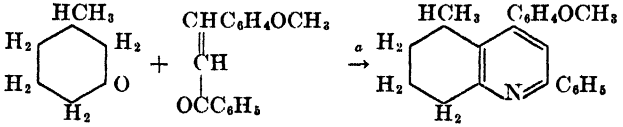
[a] Heated with RI at 100°.

Oximes of hydrindones are readily converted by a Beckmann rearrangement to dihydrocarbostyrils.[60] This type of ring enlargement, also, is general for the oximes of all cyclic ketones (see page 231).

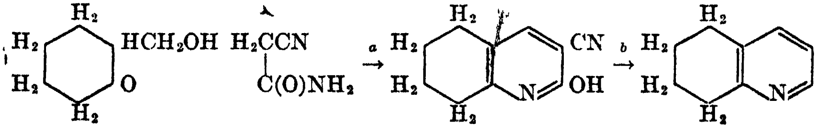


Acridines and phenanthridines can also be degraded by oxidation to quinoline dicarboxylic acids. The process parallels that which relies on the stability of a pyridine ring to survive the oxidation of quinoline.

Synthesis by Methods Used for Pyridine.—The fourth general method employs reactions that are analogous to some of those used for the preparation of pyridines. Methylcyclohexanone,[61] for example, condenses with a benzalacetophenone in a manner similar to the Knoevenagel pyridine synthesis (see page 187). Hydroxymethylenecyclohexanone condenses with cyanacetamide[62] according to the scheme below.



[a] Alc. NaOH, H₂NOH, heat.



[a] The starting material is derived from cyclohexanone, amyl formate, and sodium. The condensation with cyanacetamide occurs under the influence of piperidine. [b] Hot conc. HCl, PCl₅, Zn + HCl.

The product is convertible to 5,6,7,8-tetrahydroquinoline.[63]

These procedures are based on the fact that, in general, cyclohexanone behaves as do aliphatic ketones.

---

[59] Pictet, *Ber.*, **38**, 1946 (1905).

[60] Kipping, *J. Chem. Soc.*, **65**, 480 (1894).

[61] Stobbe, *Ber.*, **35**, 3978 (1902).

[62] Sen Gupta, *J. Chem. Soc.*, **107**, 1347 (1915).

[63] v. Braun and Lemke, *Ann.*, **478**, 191 (1930).

Reactions of Quinoline.—The chemical behavior of quinoline and quinoline compounds is a mixture of well-known reactions in the benzene and in the pyridine series, modified only by the presence of the other ring as a substituent. Reagents that will attack benzene in preference to pyridine will, naturally, be apt to attack the benzene half of quinoline. Hence the nuclear substitutions are generally less important than synthetical methods for the formation of new compounds, which have substituents in the pyridine nucleus.

The active positions in substitution processes are the 5-, and 8-, sometimes called the "ana" and "ortho." For example, quinoline nitrate added to strong sulfuric acid and allowed to stand for 1 hr. without heat yields a mixture of 5- and 8-nitroquinoline.[64] Dinitration with hot nitric acid yields the 5,7- or 6,8-dinitroquinoline.[65] Nitrations with nitrogen dioxide in carbon dioxide as a gaseous diluent give the 7-nitro compound at 95 to 100° and the 5,7-dinitro product[66] at 155 to 160°.

Sulfonation takes place in the benz nucleus. Otherwise the reactions parallel closely those in naphthalene. With concentrated acid at 220 to 230°, substitution is ortho; at 300°, it is para (*i.e.*, at C_6). The ortho product changes at 300° to the para.[67] With fuming acid, the reaction begins at a lower temperature and at 125 to 130° substitutes at C_5 and C_8 and some at C_7. At 170 and 180°, the 5- and 8- products only are formed.[68]

Direct halogenation of quinoline proceeds with some difficulty. At 160°, with sulfur dichloride, the β-chloro derivative is produced. So also is the β-bromo compound formed by heating with sulfur and bromine at 200°.[69]

Acylation is so difficult that it is necessary to introduce some labilizing groups, such as hydroxy, into the benzene half of the molecule. With the hydroxyl in the 8-position, the acyl group enters the 5-position[70] in accordance with expectations.

Oxidation of quinoline with alkaline potassium permanganate yields quinolinic acid.[71] Even when the benzene half is stabilized by a nitro group, the pyridine ring is preserved.[72] Oxidation with hypochlorous acid, however, causes formation of carbostyril[73] by an oxidation process that probably involves addition and elimination steps.

---

[64] Koenigs, *Ber.*, **12**, 449 (1879), Dufton, *J. Chem. Soc.*, **61**, 783 (1892); Meigen, *J. prakt. Chem.* [2], **77**, 472 (1908).

[65] Kaufmann and Hüssy, *Ber.*, **41**, 1735 (1908).

[66] Shorigin and Topchiev, *ibid.*, **69**, 1874 (1936).

[67] v. Georgievics, *Monatsh.*, **8**, 577, 639 (1887).

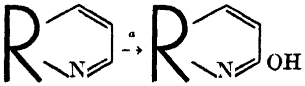
[68] LaCoste and Valeur, *Ber.*, **20**, 95 (1887); Claus, *J. prakt. Chem.* [2], **37**, 258 (1888); Fischer, *Ber.*, **20**, 731 (1887).

[69] Edinger and Lubberger, *Ber.*, **29**, 2456 (1896); *J. prakt. Chem.* [2], **54**, 355 (1896).

[70] Matsumara, *J. Am. Chem. Soc.*, **52**, 4432 (1930); **57**, 124 (1935).

[71] Hoogewerff and van Dorp, *Ber.*, **12**, 747 (1879); *Rec. trav. chim.*, **1**, 107 (1882).

[72] Claus and Kramer, *Ber.*, **18**, 1243 (1885).

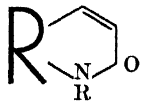


[a] Addition of HOCl to C$=$N, elimination of HX.

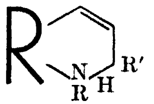
Amination with sodamide, alkylation with lithium alkyls, and other reactions are essentially the same as with pyridine. So also are the methods for ring opening.

The salts of quinoline behave, in general, as do those of pyridine. The methiodide,[74] for example, changes to N-methyl-α-quinolone (*A*) when treated with silver oxide followed by potassium ferricyanide; forms a dialkyl dihydroquinoline (*B*) with the Grignard reagent, R′MgX; produces a γ-cyanodihydro compound (*C*) with potassium cyanide which on oxidation with iodine yields

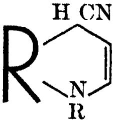
A



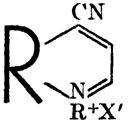
B



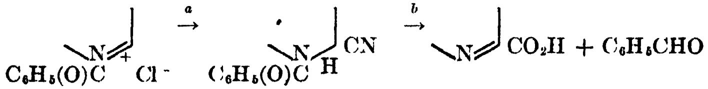
C



D



4-cyanoquinoline methiodide (*D*). The behavior of the benzoyl chloride addition compound with potassium cyanide is different in that the 2-cyano compound, instead of the 4-cyano, is produced (see page 293).



[a] KCN. [b] HCl at room temperature.

Quinoline undergoes an interesting reaction when fused with potassium hydroxide at 250 to 260°.[75] The product is the α-hydroxy derivative, carbostyril; and the process is as if potassium hydroxide adds across the C$=$N link and the product undergoes aerial oxidation. The reaction is similar, in principle,[76] to the addition of potassium hydroxide to nitrobenzene and other reagents.

---

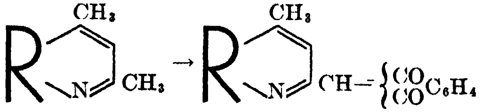
[73] Erlenmeyer and Rosenhek, *ibid.*, **18**, 3295 (1885); Einhorn and Lauch, *ibid.*, **19**, 53 (1886).

[74] Meisenheimer and Schutze, *ibid.*, **56**, 1353 (1923); Kaufman and Widmer, *ibid.*, **44**, 2058 (1911); Spath and Brunner, *ibid.*, **57**, 1243 (1924); Kondo and Ikawa, *J. Pharm. Soc. Japan*, **51**, 702 (1931); *C.A.*, **26**, 988 (1932).

[75] Chichibabin and Kursanova, *J. Russ. Phys. Chem. Soc.*, **62**, 1211 (1930); *C.A.*, **25**, 2727 (1931).

[76] Morton, *Chem. Rev.*, **35**, 1 (1944).

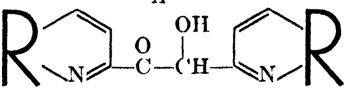
The effect of the pyridine system on the lability of methyl, halogen, and other substituents in the pyridine nucleus is that which would be predicted from a consideration of the ammonia aldehyde structure already discussed (page 194). Phthalines, for example, are formed



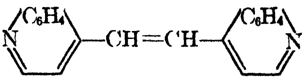
readily. Aldehydes and other agents, with an active carbonyl group, condense with the active methyl group.

Since selenium dioxide oxidizes methylene groups adjacent to carbonyl to a ketone,[77] it is not surprising that selenium dioxide in hot xylene solution oxidizes quinaldine to 2-aldehydoquinoline.[78] Likewise, lepidine and 6-methoxylepidine yield the 4-aldehydo-compounds.[79] The selenium dioxide should be prepared shortly before use or should be sublimed immediately after preparation if stored.[80] Otherwise, the yield of aldehyde is decreased. Quinaldine is converted to a benzoin (*A*), lepidine to an ethylenic product (*B*) as by-products of such oxidations.

A



B



The three hydrogen atoms of the methyl group of 2-methylquinoline are replaceable by bromine. The tribromo product hydrolyzes normally with aqueous sulfuric acid to quinaldinic acid and reduces with stannous or titanous chloride to ω-dibromo- or ω-monobromoquinaldine. These last two compounds have the unusual property, however, of resisting hydrolysis even with oleum at 50° for 12 hr. Aqueous alcoholic silver nitrate produces the expected aldehyde and alcohol respectively.[81]

The quinoline nucleus causes the elimination of more halogen than does the phenyl group in the attempted dehydrobromination of the compound analogous to dibromocinnamic acid.

$$C_9H_6N{\cdot}CH(Br){-}CH(Br)CO_2H \xrightarrow{a} C_9H_6N{\cdot}CH{=}CHCO_2H$$

[a] Aqueous KOH, Na_2CO_3, alcoholic KOH, boiling H_2O, or pyridine.

In the aromatic series, the product of this reaction is a mixture of 37 per cent ω-bromstyrene, 34 per cent cinnamic acid, and 15 per cent of α-bromo-cinnamic acid. In the heterocyclic series, the corresponding process leads only to the β(2-quinolyl)-acrylic acid,[82] *i.e.*, all the bromine is lost.

---

[77] RILEY, MOREHEY, and FRIEND, *J. Chem. Soc.*, 1875 (1932).

[78] MONTI, *Atti accad. Lincei*, **18**, 505 (1933); *C.A.*, **28**, 4733 (1934).

[79] KWARTLER and LINDWALL, *J. Am. Chem. Soc.*, **59**, 524 (1937).

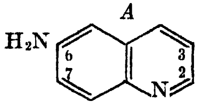
[80] KAPLAN, *ibid.*, **63**, 2654 (1942).

[81] HAMMICK, *J. Chem. Soc.*, **123**, 2882 (1923); 1302 (1926).

Resonance.—Data from heats of combustion show that there is considerable resonance in the quinoline system. The chemical reactions, however, are as if the double bonds were fixed, a fact that would follow if resonance greatly favored one structure. The reactivity of the 2- and 4-methyl groups[83] accords with this general principle.

This problem of a "static bond" has been tested by the principle that coupling should occur on the carbon atom, adjacent to, or conjugated with, an activating amino or phenolic group. In other words, if the bonds are fixed as in (*A*), coupling will occur at the 5-position; if as in (*B*), it will occur at the 7-position. Other positions can be judged similarly.[84]

A



B

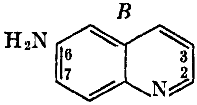


Table I gives the position of the amino group, and the positions of expected and realized coupling. Results are in general agreement with the notion of limited resonance or of restricted bonds as shown in (*A*).

TABLE I.—COUPLING REACTION WITH AMINOQUINOLINES

Position of NH_2 group	Coupling	
	Expected	Observed
2	2	2 (Diazoamino products)
3	4	4
4	3	Failed (no reaction)
2,4	3	2(?)
5	8 or 6	8 and 6
6	5	5
7	8	8
8	5 or 7	5

COMPOUNDS

Quinoline and Its Homologues.—*Quinoline* was first observed and named when Gerhardt,[85] in 1842, destructively distilled quinine over potassium hydroxide and isolated the base as the chloroplatinate. It was subsequently observed by Runge[86] among the products of distillation of coal tar. 2-Methylquinoline[87] has also been derived from the latter source. More recently, a considerable number of homologues of quinoline have been isolated from petroleum. These "kero" bases[88] have one methyl at C_2 with methyl or alkyl groups at C_3, C_4 or C_8. The compounds are prepared in the laboratory by such conventional syntheses as the Skraup and the Döbner and Miller, which were discussed earlier in this chapter. Some physical properties of quinoline and its methyl homologues are listed in Table II. Quinoline has a characteristic and

---

[82] ALBERTS and BACHMAN, *J. Am. Chem. Soc.*, **57**, 1284 (1935).

[83] MILLS and SMITH, *J. Chem. Soc.*, **121**, 2724 (1922).

[84] RENSHAW, FRIEDMAN, and GAJEWSKI, *J. Am. Chem. Soc.*, **61**, 3322 (1939); *cf.* LEFÈVRE and LEFÈVRE, *J. Chem. Soc.*, 1470 (1935).

[85] GERHARDT, *Ann.*, **42**, 310 (1842); **44**, 279 (1842).

[86] RUNGE, *Ann. Phys. Chem.*, **31**, 64 (1834).

TABLE II.—PHYSICAL PROPERTIES OF QUINOLINE AND SOME OF ITS HOMOLOGUES

Quinoline substituents	M.p., °C.	B.p., °C.	Pressure, mm.	Common derivative	M.p., °C.	Ref.
None	−19.5	238	760	Picrate	203	
2-Methyl-[a]........	−2 to −1	246–247	760	Picrate	191	89
3-Methyl..........	16–17	259.6	760	Picrate	187	96
4-Methyl[b].........	9–10	258–260	760	Picrate	208	90
5-Methyl..........	19	264	753	Picrate	218	91
6-Methyl[c].........	−22	258.6	760	Picrate	229	92
7-Methyl[d].........	39	257.6	760	Picrate	237	93
8-Methyl[e].........	....	247.8	760	Picrate	200	93
2-Ethyl...........	....	256.6	...	Picrate	146–147	94
4-Ethyl...........	....	271–274	..	Mercuric chloride	154	94
2,3-Dimethyl......	67	273	750	Picrate	231	95
2,4-Dimethyl......	....	274	756	Chloroplatinate	229	95
2,8-Dimethyl......	23.2–23.6	252	745	Phthaline	283 d.	96
3,4-Dimethyl......	65	290	737	Chloroaurate	177	97
4,6-Dimethyl......	....	280	754	Chloroamide	192 d.	97
4,7-Dimethyl......	....	283	750	Chloroplatinate	227 d.	97
4,8-Dimethyl......	....	273	751	Chloroaurate	220 d.	97
5,8-Dimethyl......	4–5	265	736	Dichromate	149	98
6,8-Dimethyl......	....	268–269	...	....	.....	99
2,3,8-Trimethyl....	55–56	280	747	Picrate	242 d.	100
2,4,8-Trimethyl....	....	280	746	Picrate	193	100

Trivial names (*a*) Quinaldine, (*b*) lepidine, (*c*) *p*-methylquinoline, (*d*) *m*-methylquinoline, (*e*) *o*-methylquinoline.

[89] WALLACH and WÜSTEN, *Ber.*, **16**, 1008 (1883), CIAMICIAN and SILBER, *ibid.*, **38**, 3816 (1905). TIMMERMANN, HENNANT-ROLAND, *J. Chem. Phys.*, **34**, 693 (1938).

[90] KNORR, *Ann.*, **236**, 94 (1886); BEYER, *J. prakt. Chem.* [2], **34**, 393 (1886)

[91] GABRIEL and THIEME, *Ber.*, **52**, 1079 (1919).

[92] SKRAUP, *Monatsh.*, **2**, 139 (1881).

[93] SKRAUP and BRUNNER, *ibid.*, **7**, 140 (1886).

[94] REBER, *Ber.*, **19**, 2996 (1886).

[95] BIGGS and BAILEY, *J. Am. Chem. Soc.*, **55**, 4141 (1933).

[96] LAKE and BAILEY, *ibid.*, **55**, 4143 (1933).

[97] KNORR, *Ann.*, **245**, 357 (1888).

[98] LELLMANN and ALT, *Ann.*, **237**, 307 (1887).

[99] LEEDS, *J. Am. Chem. Soc.*, **5**, 1 (1883).

[100] PERRIN and BAILEY, *ibid.*, **55**, 4136 (1933).

---

[87] JACOBSEN and REIMER, *Ber.*, **16**, 1082 (1883).

[88] SCHENCK and BAILEY, *J. Am. Chem. Soc.* **63**, 1364, 1365 (1941).

penetrating odor and exhibits marked physiological properties. The higher homologues share these characteristics, but to a less degree.

2-Phenylquinoline,[101] melts at 84° and boils at 363°.

Reduced Quinolines.—*Tetrahydroquinoline,* prepared by reduction of quinoline, behaves as if it were an N-substituted aniline compound.[102] Its N-nitroso derivative readily undergoes rearrangement under the influence of alcoholic hydrochloric acid to the para position. It also gives dyestuff as does any alkylated aniline.[103] Nitration of its salt yields a 7-nitro compound as predicted for a meta-orienting ammonium salt.[104]

Kairolin (b.p. 247 to 250°) is the trade name for N-methyltetrahydroquinoline.[105] It is prepared by reduction of quinoline methiodide with tin and hydrochloric acid. The compound has an antipyretic action. Kairolin does not undergo ring scission with cyanogen bromide, although the higher members of the series are cleaved. Hydrogen peroxide forms an N oxide that can be separated into its optical antipodes by means of the *d*-bromocamphorsulfonic salt.[106]

Nitro, Sulfonic Acid, and Halogen Derivatives.—These substituted quinolines are either prepared by nitration, sulfonation, or halogenation, or by synthesis. Frequently, both methods are used in order to determine the position taken by a substituting reagent. For example, nitration gives the 5- or 8-nitro derivative, which in turn can be obtained by an appropriate Skraup synthesis from a nitroaniline. Since the nitro can be converted to an amino and thence to a hydroxy group, the position of the sulfonic acid, likewise convertible to a hydroxy group, is determined. By such conventional methods, the positions taken by entering groups have been well established.

Halogen-substituted quinolines are obtained by such common reactions as conversion of a hydroxy to a chloro compound with phosphorus pentachloride, by diazotization of an amino group followed by the usual steps, or by treatment of a quinoline with a peracid followed by chlorination of the N-oxide[105b] to give a 2- or 4-chloro product. Except for greater reactivity exhibited in the 2- and 4-positions, the reactions of the halogen compounds are the usual ones observed in the aromatic series.

---

[101] (*a*) Murmann, *Chem. Zeit.*, **7**, 273 (1904); *Chem. Centr.*, II, 454 (1904); (*b*) Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

[102] Bamberger, *Ann.*, **257**, 21 (1890); Bamberger and Wurtz, *Ber.*, **24**, 2055 (1891); Eibner, *ibid.*, **29**, 2980 (1896).

[103] Döbner and Miller, *Ber.*, **16**, 2468 (1883); v. Braun and Aust, *ibid.*, **49**, 505 (1916); v. Braun, *ibid.*, **49**, 1104 (1916).

[104] v. Braun, Grabowski, and Rawicz, *ibid.*, **46**, 3169, 3173 (1913).

[105] Hofmann and Koenigs, *ibid.*, **16**, 727 (1883); Feer and Koenigs, *ibid.*, **18**, 2388 (1885).

[106] Meisenheimer, *Ann.*, **385**, 117 (1911).

Hydroxyquinolines.—*2-Hydroxyquinoline* (m.p. 199 to 200°), known also as *carbostyril*, can be prepared by (*a*) ammonium sulfide reduction of *o*-nitrocinnamic acid,[27] (*b*) reaction of quinoline and hypochlorous acid,[73] (*c*) fusion of quinoline with potassium hydroxide.[75]

This compound exhibits the customary tautomerism[107] of hydrogen between nitrogen and oxygen. For example, ethyl iodide with the silver salt gives the O-ether; with the sodium salt it gives the O- and N-ethers. The compound is insoluble in ammonium hydroxide but soluble in sodium hydroxide. There is no color with ferric chloride. Phosphorus pentachloride yields α-chloroquinoline, which in turn changes to quinoline when reduced with hydrogen iodide. Permanganate oxidation gives isatinic, *o*-$H_2NC_6H_4C(O)CO_2H$, and oxalylanthranilic acids, $HO_2CC_6H_4NHC(O)CO_2H$.

8-Quinolinol.—This compound (m.p. 75 to 76°, b.p. 267°) is known also as 8-hydroxyquinoline. Since the hydroxy group is in the benz ring, the compound can be prepared by any one of the conventional methods used for making aromatic compounds such as sulfonation with oleum and fusion of the salt with sodium hydroxide[108,109] at 225°, or chlorination and hydrolysis of the chloro compound with caustic[110] at 200 to 300° in the presence of copper oxide.

8-Quinolinol forms a large number of complexes with inorganic metals which are useful for analysis. For example, the copper, zinc, or cadmium complex will precipitate[111] in sodium acetate solutions when the quantity present is as small as 1 part in 630,000, 1,000,000, and 416,000, respectively. Aluminum, bismuth, uranium, manganese, ferric iron, cobalt, and nickel are precipitated when present in larger amounts, of the order of 1 part in 310,000 to 250,000. Magnesium forms a precipitate from ammonia solution. The crystals are valuable for gravimetric analysis but are not very satisfactory for characterization in microanalysis, since the different metal complexes have similar appearing crystals.[112] The structure of the copper complexes is illustrated below. The similar chelation of hydrogen in 8-quinolinol accounts for its volatility in steam.

---

[107] Friedländer and Müller, *Ber.*, **20**, 2009 (1887); Knorr, *ibid.*, **30**, 930 (1897); Bogert and May, *J. Am. Chem. Soc.*, **31**, 508 (1909); Kaufmann and de Petherd, *Ber.*, **50**, 344 (1917).

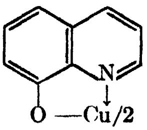
[108] Weidel and Cobenzyl, *Monatsh.*, **1**, 862 (1880).

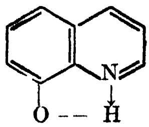
[109] Magidson and Rubtzov, *Khim. Farm. Prom.*, No. 1, 20 (1935); *C.A.*, **30**, 1789 (1936).

[110] v. Vorozhtsov, Jr., and Mitzengendler, *J. Gen. Chem.* (*U.S.S.R.*), **6**, 63 (1936); *C.A.*, **30**, 4862 (1936).

[111] Berg, *J. prakt. Chem.*, **115**, 178 (1927).

[112] Rosenthaler, *Mikrochemie*, **13**, 317 (1933).



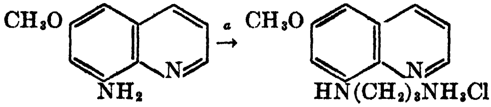


The principle of metal complex formation has been used in chromatographic adsorption on 8-quinolinol[113] whereby the anions are distinguished by their colored zone in the chromatogram, *e.g.*, VO_3^- gray black, WO_4^{--} yellow, Cu^{++} green, Bi^{+++} yellow, Ni^{++} green, Co^{++} red, Zn^{++} yellow with intense green fluorescence, Fe^{+++} black, and UO_2^{++} reddish orange.

8-Quinolinol with hydroxylamine in 2 *N* sodium carbonate gives 5-amino-8-hydroxyquinoline.[114] In the presence of excess quinolinol, atmospheric oxygen converts the product to 5,8-quinolinequinone-5-(8-hydroxyquinolylimide). The green color so produced is a very delicate test for hydroxylamine.

8-Quinolinol in boiling ethanol with iodine gives two mono-iodo compounds or a 5,7-diiodoquinoline.[115] The sulfate of 8-quinolinol is sometimes used in medicine as a spermatocide under the name of quinosol.[116] 8-Hydroxy-7-iodoquinoline-5-sulfonic acid, mixed with sodium acid carbonate, is sold under the name of Chiniofon, Yatren, or Quinoxyl. It is prepared from 8-quinolinol by iodination and sulfonation.

Aminoquinolines.—Amino derivatives of quinoline are prepared by reduction of nitro groups (if in the benzene nucleus), by amination with sodamide, by ammonolysis of a halogen derivative, or by reduction of a diazo compound. Many amino derivatives have therapeutic activity. For example, *8-amino-6-hydroxyquinoline*, though itself inactive toward malaria, forms N-aminoalkyl derivatives that are valuable as substitutes for quinine. A typical preparative method is shown below. The first step introduces the alkyl chain by means of a bromo alkyl phthalimide reagent. The second step of hydrolysis of the phthalimide derivative is usually effected by dilute acid at relatively high temperatures, but



[a] $Br(CH_2)_3N{=}C_6H_4O_2$, H_2NNH_2 in order to form the phthalhydrazide, hydrolysis with aq.HCl.

---

[113] Erlenmeyer and Dahn, *Helv. Chim. Acta*, **22**, 1369 (1939).

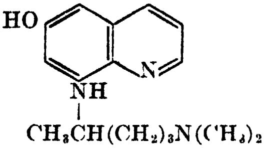
[114] Berg and Becker, *Ber.*, **73**, 172 (1940).

[115] Pirrone and Cherubino, *Atti accad. Lincei*, **18**, 311 (1933); *C.A.*, **28**, 3073 (1934); Zeifman, *Trans. Inst. Pure Chem. Reagents* (*U.S.S.R.*), **16**, 80 (1939); *C.A.*, **34**, 3745 (1940).

[116] Goodman and Gilman, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

hydrazine readily converts the imide to an aminophthalhydrozide, which is hydrolyzed very easily in the third step.[117]

Plasmoquine, 6-hydroxy-8-(δ-dimethylamino-α-methyl butyl)-aminoquinoline, is one of the substitutes for quinine. It derives its name because of its plasmocidal action. It kills sexual malaria parasites but does not cure malaria.[118]

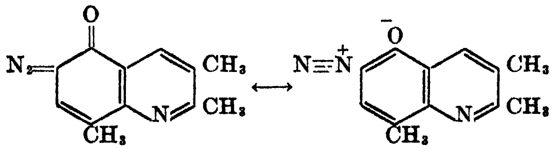


The variation of activity of such compounds with structural change[119] is well illustrated in Table III.

TABLE III.—EFFECT OF SUBSTITUENTS IN QUINOLINE ON THERAPEUTIC ACTIVITY

Substituent in position		Therapeutic index
6	8	
CH_3O	$(C_2H_5)_2NCH(CH_3)CH_2CH_2NH—$	25
CH_3O	$(C_2H_5)_2NCH(CH_3)CH_2NH—$	2
Cl	$(C_2H_5)_2NCH_2CH_2CH_2NH—$	2.5
CH_3O	$(C_2H_5)_2NCH_2CH_2CH_2NH—$	16.5
CH_3O	$H_2NCH_2CH_2CH_2NH—$	13.3
HO	$(C_2H_5)_2NCH_2CH_2CH_2NH—$	18.5

Quinolinediazoxides.—5-Hydroxy-2,3,8-trimethylquinoline, isolated as the hydrobromide (brick-red needles that melt at 330 to 335°), is obtained from 2,3,8-trimethylquinoline. Nitration of this hydroxy compound or of its methyl ether introduces a nitro group in the 6-position and reduction by stannous chloride of the nitromethoxy product, in turn, produces 6-amino-5-hydroxy-2,3,8-trimethylquinoline. Diazotization of this last product produces a deep-red diazo oxide. which possibly has the resonance formula shown below.



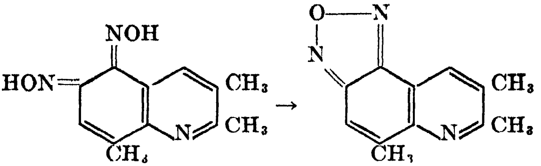
---

[117] BALDWIN, *J. Chem. Soc.*, 2059 (1929).

[118] OETTINGER, "Therapeutic Agents of the Quinoline Group," Chemical Catalog Company, Inc., New York, 1933.

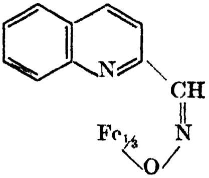
[119] MAGIDSON and BOBYSHEV, *J. Gen. Chem., U.S.S.R.*, **8**, 899 (1938); *C.A.*, **33**, 1327 (1939).

Such a compound[120] is alkali-insoluble, is stable to long boiling in ethanol, and is convertible to 5-hydroxy-2,3,8-trimethylquinoline by elimination of nitrogen under the reducing influence of an alkaline solution of sodium hydrosulfite. When a pyridine solution of the diazooxide is boiled with an alcoholic solution of hydroxylamine hydrochloride, the dioxime is obtained and this compound, in turn, is converted to a furanoquinoline by hot 10 per cent sodium hydroxide.

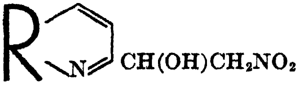


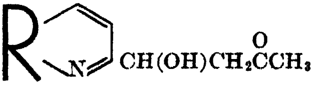
Formation of these diazooxides, *i.e.*, internal diazoanhydride, is apt to occur whenever an *o*- or *p*-aminophenol is converted to a diazonium salt and the acidity of the medium is diminished.[121]

Aldehydes, Ketones, and Acids.—2-*Aldehydo*- and 4-*aldehydo-quinoline* are most conveniently prepared by oxidation of the corresponding methyl derivative with selenium dioxide as described before. Quinoline-2-aldoxime forms chelated metal compounds and therefore has a cis-configuration.[122] The oximes of 3,8-dimethyl-2-acetyl- or 2-propionyl-quinoline, however, show no reaction with metallic ions.[123]



The aldehydo compounds yield the ordinary derivatives such as the oxime and phenylhydrazones. They also yield β-hydroxy-β-quinolyl-α-nitroethanes when treated with nitromethane and a few drops of diethylamine.[78] Similarly, mono- and di-condensation products are produced with acetone under the influence of 10 per cent caustic soda solution.





---

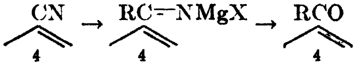
[120] Modlin, Jr., and Burger, *J. Am. Chem. Soc.*, **63**, 1115 (1941).

[121] Morgan and Tomlins, *J. Chem. Soc.*, **111**, 497 (1917). See, however, Staudinger, *Helv. Chim. Acta*, **4**, 239 (1921).

[122] Taylor, Winckles, and Marks, *J. Chem. Soc.*, 2778 (1931).

[123] Burger and Modlin, Jr., *J. Am. Chem. Soc.*, **62**, 1079 (1940).

Ketones can be prepared conveniently by treating the aldehyde with diazoalkanes.[123] For example, 3,8-dimethyl-2-aldehyde condenses with diazomethane, and better with diazoethane, to form the corresponding 3,8-dimethylquinolyl methyl and ethyl ketones. Ketones can also be obtained by allowing a Grignard reagent to react with the nitrile,[124] as shown by partial formulas below.



Carboxylic acids are obtained by a variety of conventional processes. Oxidation of methyl groups by chromic or chromic-sulfuric acid is frequently used. Another process is the condensation of an active methyl group with an aldehyde, followed by ozonolysis and oxidation of the styryl product. Sulfonation followed by conversion to the nitrile and hydrolysis is useful for preparing acids with the carboxyl group attached to the aromatic nucleus. The Skraup synthesis with aminobenzoic acids or with toluidines (the methyl group is subsequently oxidized) is valuable.

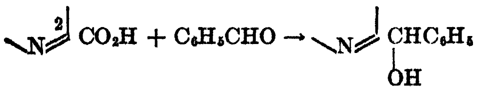
TABLE IV.—PHYSICAL PROPERTIES OF SOME QUINOLINE CARBOXYLIC ACIDS

Position of Carboxyl Groups	M.P., °C.
2[a]	157
3	275 d.
4[b]	253–254
5	338
6	290–291
7	248–249
8	186–187.5
2,3[c]	120–130 d.
2.4	246 d.

Common names (a) quinaldinic acid, (b) cinconinic acid, (c) acridinic acid.

As would be expected, a carboxyl group, α or γ to the nitrogen atom, is thermally unstable. Loss of one equivalent of carbon dioxide at the decomposition point can be expected as part of the behavior of such acids.[125]

Decarboxylation of quinaldinic acid (and also of isoquinaldinic and α-picolinic acid) in the presence of benzaldehyde, acetophenone, or benzophenone causes the formation of a carbinol according to the equation



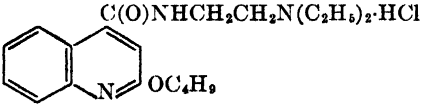
---

[124] KAUFMANN, KUNKLER, and PEYER, *Ber.*, **46**, 3573 (1913).

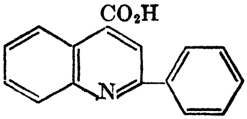
[125] JOHNSON and ADAMS, *J. Am. Chem. Soc.*, **45**, 1307 (1923).

Such a reaction occurs only in the case of these acids. It is explained[126] on the basis that the system, N=C, is essentially the cyanide ion N≡C with one of the three bonds replaced by a ring and that a reaction analogous to cyanohydrin formation occurs during decarboxylation.

2-Alkoxy-cinchoninic Acid Aminoalkylamides.—Compounds of this type have an anesthetic reaction. The potency depends on the size of the alkoxy group and on the number of methylene groups between the amide and dialkylamino groups[127] (*cf.* cocaine, page 249). Nupercaine, also known as Percaine, is 2-butoxy-N-(β-diethylaminoethyl) cinchoninamide hydrochloride and is a local anesthetic of high potency and high toxicity.[128] It is made from α-butoxycinchoninic acid and ethylene diamine, with subsequent ethylation of the amino group.



Nupercaine

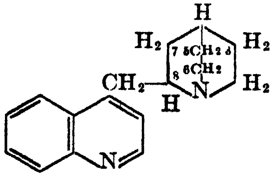


Cincophen

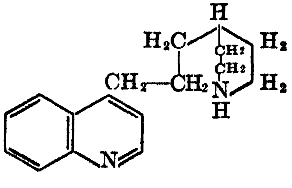
Cincophen.—This compound, sometimes called atophan, has been used as an antimalarial, although it has some tendency to damage the liver.[116] The physiological activity in this class depends on a quinoline nucleus, an aryl group at C_2, and a carboxyl group at C_4 or C_3. The quinolyl and aryl groups may have substituents, and the carboxyl group may be replaced by the amide or ester.[129] Cincophens are usually prepared by Pfitzinger's reaction (page 273). The parent compound melts at 171° and loses carbon dioxide at a little higher temperature.

The Quina Alkaloids and Related Compounds.—*Ruban*[130] is the mother substance of the quina alkaloids and has the structure shown in (*A*) below. *Rubatoxin* is similar except that one of the quinuclidine rings is opened (*B*). These names are derived from Rubiaceas, the natural source of the alkaloid, and were given by Rabe in an effort to simplify the naming of compounds related to quinine.

A



B



---

[126] Ashworth, Daffern, and Hammick, *J. Chem. Soc.*, 809 (1939).

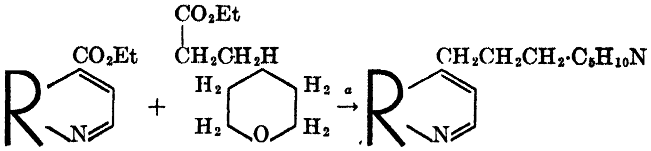
[127] Magidson, Fedotova, and Zverev, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 2097 (1939); *C.A.*, **34**, 3882 (1940).

[128] "The Merck Index"; *cf.* Ref. 116.

[129] v. Braun and Brauns, *Ber.*, **60**, 1253 (1927); Benary, *ibid.*, **66**, 1569 (1933).

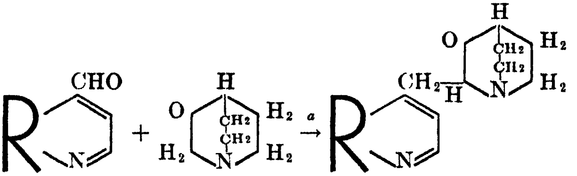
[130] Rabe, *ibid.*, **55**, 522 (1922).

The synthesis of rubatoxin[131] begins with the condensation of β-(tetrahydro-4-pyranyl)-propionic acid (see Chap. IX for derivation from γ-tetrahydropyrone) with ethyl cinchoninate by means of sodium alkoxide, and thence by conventional steps of reduction and transformation of the oxygen atom to nitrogen progresses to the desired end.



[a] NaOEt, hydrolysis and decarboxylation, Wulff reduction, fuming HBr, alc. NH_3.

One method[132] for obtaining a ruban derivative is given below.



[a] The quinolylaldehyde component is obtained from 4-methylquinoline by condensation with chloral under the influence of pyridine at 85 to 90°, treatment of the aldol product with alcoholic KOH in order to eliminate water, and to hydrolyze the halogens, careful oxidation of the sodium salt of the acrylic acid at −10° with permanganate in a mixture of chloroform and ether. The 3-keto quinuclidine component is prepared by a Dieckmann reaction as described in the previous chapter. The quinolylaldehyde and ketoquinuclidine condense with each other under the influence of piperidine acetate. The double bond is then reduced by H_2 over Pd. The 5-keto ruban can be reduced by aluminum isopropoxide to ruban-5-ol.

Quinine is 6′-methoxy-3-vinyl-9-rubanol. It is used[116] principally as an antifebrifuge and to some extent as a spermatocide, although in the latter case a reliable degree of activity is not reached except with concentrations that are not safe. Its importance as a cure for malaria has stimulated numerous chemical investigations. So much is this true that not only the name but also much of the chemistry of the quinoline compounds stems from the interest in its medicinal properties. The stimulation to chemical investigation was comparable in its day to that aroused by the discovery of the sulfa drugs in modern chemotherapy, since malaria was a scourge for which there was then no relief.

The discovery[133] of the therapeutic value of the quina alkaloids followed the Spanish conquest of Peru. It is not certain that the native Indians used it, but the Spaniards early discovered its value. An official in Ecuador is reported to have been cured of malaria in 1630. The physician to the Countess Anna del Chinchon, wife of the viceroy of Peru, is popularly supposed to have observed the marvelous cure of her illness in 1638, but this story has recently been denied because the Count's diary contains no record of such an event or that his first wife was ever in Peru. The drug was introduced in Spain in 1639; and its use spread rapidly under the name of Peruvian bark, Jesuit bark (because the Jesuit order was very active in furthering its use) and cardinal's bark. The opposition of some conservative physicians, who could not reconcile its use with the teachings of Galen, made exploitation by charlatans very profitable. The name of Jesuit bark also retarded its introduction in some quarters because of the intense religious controversy which then prevailed. Quinine is now extensively cultivated in Java where the Dutch have succeeded in increasing the yield and quality of the commercial product. About 5 per cent of the weight of the bark is quinine.

---

[131] Prelog, Seiwerth, Hahn, and Cerkovnikow, *Ber.*, **72**, 1325 (1939).

[132] Clemo and Hoggarth, *J. Chem. Soc.*, 1241 (1939).

[133] (*a*) Henry, "The Plant Alkaloids," 3d ed., The Blakiston Company, Philadelphia, 1939; (*b*) Major, "Disease and Destiny," D. Appleton-Century Company, Inc., New York, 1936; (*c*) editorial in *Chem. and Ind.*, **61**, 218 (1942).

Over 20 alkaloids[133a] have been isolated from various species of cinchona and cuprea. The most important are quinine, quinidine, cinchonine, and cinchonidine (see Table V). The structural formulas of all the twenty some alkaloids are not known.

TABLE V.—SOME CINCHONA ALKALOIDS AND DERIVATIVES

Formula	Dextrorotatory	Levorotatory	Functional change
$C_{20}H_{24}O_2N_2$	Quinidine	Quinine	
$C_{20}H_{26}O_2N_2$	Hydroquinidine	Hydroquinine	Ethyl for vinyl
$C_{19}H_{22}ON_2$	Cinchonidine	Cinchonine	Methoxy free
$C_{19}H_{22}O_2N_2$	....	Cupreine	OH for OCH_3
$C_{19}H_{24}ON_2$	Hydrocinchonidine		
$C_{19}H_{24}O_2N_2$	epi-Quinidine	epi-Quinine	

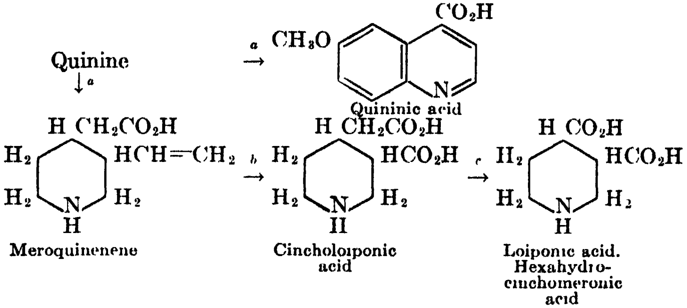
The natural cinchona alkaloids and many of their derivatives have similar pharmacological properties. Antimalarial activity[133a] is not related to the direction of rotation, although instances are known where patients are allergic to the levo- but not to the dextro-rotatory drugs. Presence of a vinyl group is unimportant. Indeed, hydroquinine (ethyl in place of vinyl) is more active than quinine; and a product free from the vinyl or ethyl group is also active.[134] Presence of the secondary alcohol between the quinoline and quinuclidine portions is essential.[135] Changes at the O-alkyl ether modify the toxicity. According to one view, the biological activity of quinine, cupreine, and related drugs may be a function of the size or space occupied by the molecule.[136]

---

[134] PRELOG, STERN, SEIWERTH, and HEIMBACH-JUHASZ, *Naturwissenschaften*, **28**, 750 (1940).

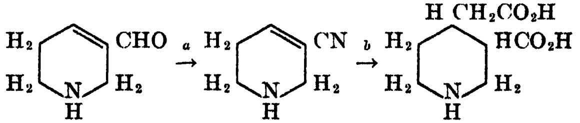
[135] RENFREW and CRETCHER, *Chem. Rev.*, **30**, 48 (1942).

Mild oxidation of quinine converts the carbinol group to a ketone, which, by vigorous oxidation, is split into quininic acid—6-methoxyquinoline-4-carboxylic acid—and a derivative of the quinuclidine half (see Fig. 2). Degradation products of the quinuclidine portion are distinguished by use of the word loipon, *e.g.*, cincholoiponic and loiponic acids, from λοιποσ, meaning "a residue," or by the prefix *mero-* from μέροσ, meaning "a portion." The structure[137] of cincholoiponic and loiponic acids was indicated by conversion to pyridine compounds and was proved by synthesis of *d*-cincholoiponic acid. The starting material is Δ^3-piperidine-β-aldehyde, itself obtained by treatment of the iminodipropionacetal, $HN(CH_2CH_2CH[OEt]_2)_2$, with fuming hydrochloric acid.



[a] Mild oxidation with CrO_3 converts the secondary alcohol group to a ketone. Vigorous oxidation by CrO_3 cleaves the system to quininic acid and meroquienene. [b] $KMnO_4$. [c] $KMnO_4$.

FIG. 2.—Products derived by oxidation of quinine.



[a] H_2NOH, $SOCl_2$. [b] 1,4-Addition of $NaCH(CO_2Et)_2$, $Ba(OH)_2$ in order to hydrolyze the nitrile, resolution by use of the brucine salt.

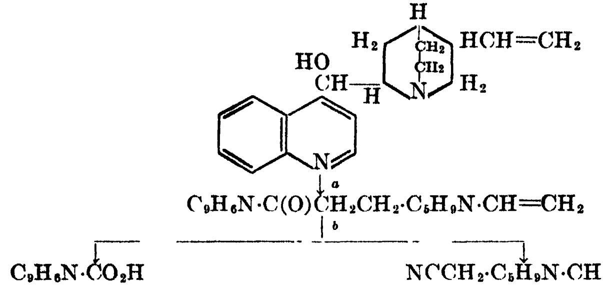
Another scheme of degradation operates through an oxime.[138] For example, the hydrosulfate salt of cinchonine (see Fig. 3) when refluxed in alkaline sodium acetate medium gives cinchonicine, otherwise known as cinchotoxine. This material, in turn, forms an isonitroso derivative with amyl nitrite. Subsequent treatment with phosphorus pentachloride cleaves the oximino system to an acid and a nitrile. A similar degradation carried out on quinotoxine, derived from quinine,[139] gives a different acid, quininic acid, but the same meroquineninenitrile.

---

[136] SLOTTA and BAHMISCH, *Ber.*, **68**, 754 (1935).

[137] WOHL and LOSANITSCH, *Ber.*, **40**, 4698 (1907); WOHL and MAAG, *ibid.*, **42**, 627 (1909).

[138] KOENIGS, *Ber.*, **40**, 648, 2873 (1907).

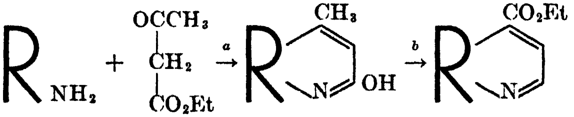


[a] Hydrosulfate salt in boiling aqueous-acetic acid and sodium acetate. [b] $C_5H_{11}ONO$, PCl_5 in $CHCl_3$.

FIG. 3.—Decomposition of cinchonine into two products.

The synthesis of quinine[140] requires (1) the preparation of the quinoline part (Q) from anisidine, (2) the formation of the piperidine part (P) from 7-hydroxyisoquinoline, and (3) the union of these two parts and the formation of the bicyclic ring system, the first and third sections by the same methods used by Rabe in his synthesis of dihydroquinine.

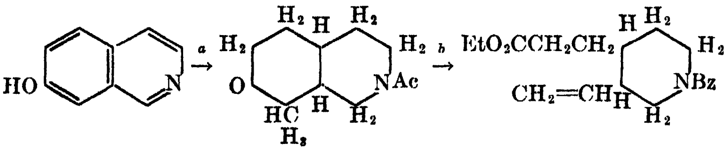
1. Quinoline part (Q).



Large R = $CH_3OC_6H_3$.

[a] Heat to form the anilide followed by ring closure with sulfuric acid. [b] $PCl_5 + POCl_3$, Al + HOAc, $C_6H_5CHO + ZnCl_2$, $KMnO_4$, HCl + C_2H_5OH.

2. Piperidine part (P).



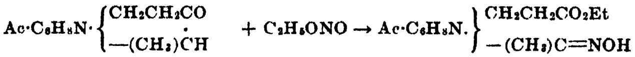
[a] Formaldehyde and piperidine (a Mannich reaction) to give a $—CH_2·NC_5H_{10}$ substituent at C_8, hydrogenation over Pt in order to form 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline, acetylation, H_2 + Raney Ni in order to form a decahydroisoquinoline, oxidation by chromic anhydride in acetic acid. The cis form (cis with respect to the hydrogens at the fusion line of the two rings) is isolated. [b] Ethyl nitrite and sodium ethoxide in order to open the ring and form the ethyl ester of N-acetyl-10-oximodihydrohomomeroquinene (see paragraph below), reduction to the 10-aminodihydro compound, $CH_3I + K_2CO_3$, in order to form a quaternary salt, alkali degradation of the quaternary salt (exhaustive methylation process) to give the vinyl group, esterification, benzoylation.

The ring opening of 7-keto-8-methyldecahydroisoquinoline by ethyl nitrite and sodium ethoxide is a novel feature in this synthesis. Ordinarily the reaction of nitrous acid with a ketone causes condensation at the methylene group and formation of an isonitroso ketone. In Knorr's pyrrol synthesis nitrous acid or amyl nitrite thus condenses on the ethyl rather than the methyl side, that is, at the carbon atom that has the fewer hydrogen atoms. In the present instance the attack of ethyl nitrite is also at the carbon atom that is lean in hydrogen atoms. Oxime formation occurs as in the equation below, but the ring is necessarily opened.

---

[139] RABE and MILARCH, *Ann.*, **382**, 365 (1911).

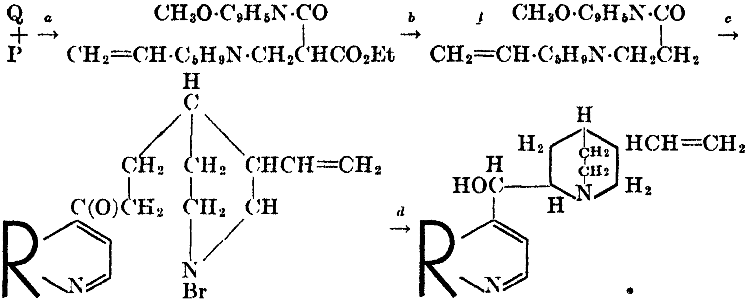
[140] WOODWARD and DOERING, *J. Am. Chem. Soc.*, **66**, 849 (1944); **67**, 860 (1945).



$$Ac{\cdot}C_6H_8N{\cdot}\left\{\begin{matrix} CH_2CH_2CO \\ \cdot \\ -(CH_3)CH \end{matrix}\right. + C_2H_5ONO \rightarrow Ac{\cdot}C_6H_8N.\left\}\begin{matrix} CH_2CH_2CO_2Et \\ -(CH_3)C{=}NOH \end{matrix}\right.$$

For other instances of similar ring cleavage in homocyclic systems, see Clarke, Lapworth, and Wechter, *J. Chem. Soc.*, **93**, 30 (1908). This over-all view of the reaction can be supplemented by more detailed pictures. The condensation of the ketone with ethyl nitrite can be regarded as one like one between two esters as in the formation of ethyl acetoacetate with subsequent alcoholysis and cleavage of the *nitroso* ketone, —C(O)—C(NO)—, product. An electronic mechanism, in which a center of anion activity forms at the tertiary carbon and attaches ethyl nitrite, after which ejection of the ethoxy ion occur together with other necessary changes, has also been written[140] for this interesting change.

3. Union of the two parts and completion of synthesis.


Q
+
P
a
$CH_3O{\cdot}C_9H_5N{\cdot}CO$
$CH_2{=}CH{\cdot}C_5H_9N{\cdot}CH_2CHCO_2Et$
b
$CH_3O{\cdot}C_9H_5N{\cdot}CO$
$CH_2{=}CH{\cdot}C_5H_9N{\cdot}CH_2CH_2$
c
H
C
CH₂
CH₂
CHCH=CH₂
C(O)CH₂
CH₂
CH
N
Br
R
N
d
H
H₂
CH₂
CH₂
HCH=CH₂
H
HOC
N
H₂
H
R
N

[a] NaOEt. The benzoyl radical is lost during this Claisen condensation. [b] Hydrolysis and decarboxylation. [c] NaOBr. [d] NaOEt, H_2 + Pd, resolution with *d*-tartrate.

The formula of *cupreine* is the same as for quinine except for the replacement of a methoxy by a hydroxy group. Hydrocupreine (ethyl for vinyl) has considerable value as an antimalarial.[118] The ethyl ether, in the form of the hydrochloride, is known as Optochin hydrochloride.[128] It is a specific against progressive infection with pneumococci.[141] In the large doses often necessary to influence the course of pneumonia, it is apt to be toxic or cause severe eye disturbances. The toxic character is reduced by alkylation of the potassium salt of hydrocupreine[142] with ethylene chlorohydrin, glycol mono-*p*-toluene sulfonate, or *β*-chloroethyl vinyl ether in accord with the general opinion that compounds with an alcoholic hydroxyl group are less toxic than the corresponding hydrocarbon.

When cupreine is methylated, the product is quinine; but when quinine is demethylated with hydrochloric or sulfuric acid, the product is an isomer of cupreine, called apoquinine or *β*-isocupreine.[143] This

[141] Morgenroth, *Naturwissenschaften*, No. 26, 1913; *C.A.*, **8**, 182 (1914).

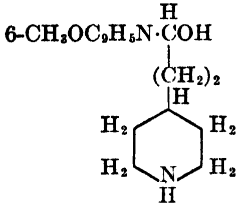
[142] Butler, Nelson, Renfrew, and Cretcher, *J. Am. Chem. Soc.*, **57**, 575 (1935).

[143] Jarzynski, Ludwiczakowna, and Suszko, *Rec. trav. chim.*, **52**, 839 (1933); Henry and Solomon, *J. Chem. Soc.*, 1923 (1934); *Chemistry & Industry*, **54**, 641 (1935).

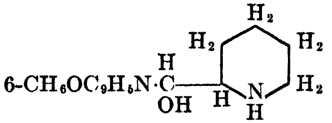
compound[144] differs from cupreine in that the vinyl has isomerized to an alkylidene radical, $\rangle\!=\!CHCH_3$. The alkyl ethers of these compounds have also a marked antipneumococcic activity.[145] The β-hydroxy-*n*-propyl ether has a very strong bacteriostatic action and a lower toxicity than the alkyl derivative.

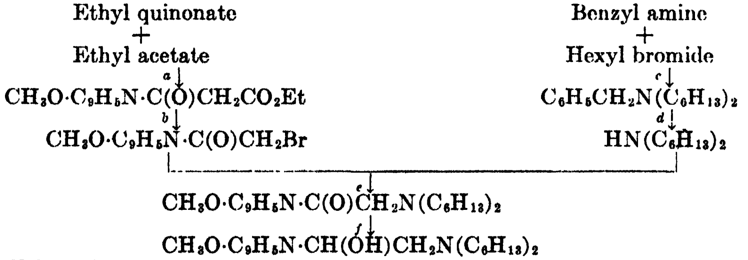
Dihydroquinicinols (*d* and *l*)[146] are γ-piperidine derivatives, as in (*A*), which have a close resemblance to dihydroquinine. Nevertheless, they are devoid of any significant antiplasmodial action when tested on bird malaria. If, however, the piperidine ring is attached at its alpha position, as in (*B*), the two diastereoisomerides obtained are both active. The difference between these two compounds lies in the number of carbon atoms between the quinoline nucleus and the disubstituted nitrogen in the piperidine ring. In fact, it is possible, as shown below, to prepare compounds with antimalarial activity that differ from quinine in the matter of the quinuclidine ring but still have two carbon atoms between the secondary nitrogen and the quinoline nucleus.

A



B





[a] $NaNH_2$. [b] Hydrolysis with 25 per cent H_2SO_4, bromination with Br_2 in $CHCl_3$. [c] KOH. [d] $H_2 + PtO_2$ in glacial HOAc at 70°. [e] Reaction in hot aniline. [f] $H_2 + PtO_2$.

The dibutyl, diamyl, and dihexyl compounds are active; lower and higher homologues are inactive.

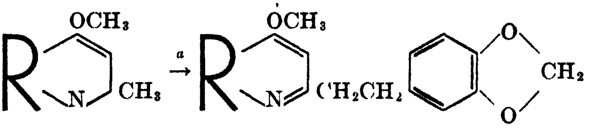
---

[144] This compound has also been called apocupreine. The latter designation does not conform[143] to the common meaning of the prefix *apo-*, since isocupreine is not derived from cupreine but from quinine.

[145] Butler, Renfrew, Cretcher, and Souther, *J. Am. Chem. Soc.*, **59**, 227 (1937); Green, Renfrew, and Butler, *ibid.*, **61**, 1783 (1939).

[146] King and Work, *J. Chem. Soc.*, 1307 (1940); Work, *ibid.*, 1315 (1940).

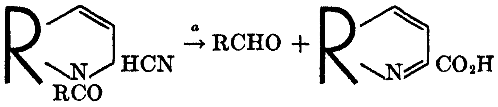
Cusparine.—The bark of *Cusparia trifoliata, Engl* is used as a bitter principle in medicine.[133a] It contains quinoline, 2-methylquinoline, 1-methyl-2-quinolone, 2-dihydroquinoline, 2-amylquinoline, cusparine, galipine, and other alkaloids.[147]



[a] Piperonal + $ZnCl_2$ at 125°, H_2 over Pd on carbon.

Synthesis of *cusparine* is effected by catalytic reduction of the condensation product of 4-methoxyquinaldine with piperonal.[148] *Galopine* has the same structure except for two methoxy groups in place of a methylenedioxy group.

Acyl-1,2-dihydroquinaldonitriles.—These compounds are intermediates in the conversion of an acid chloride to an aldehyde.[149] They are obtained by addition of a benzene solution of the acid chloride to a solution of dry hydrogen cyanide in quinoline at −5°. The mixture is allowed to stand about 16 hr. in order to allow quinoline hydrochloride to separate. The nitrile is readily hydrolyzed with 5 to 10 *N* sulfuric acid to quinaldinic acid and an aldehyde. Typical yields of aldehyde are 96 per cent for benzaldehyde to 77 per cent for *p*-chlorobenzaldehyde, to 64 per cent for isovaleral and 10 per cent for propional.

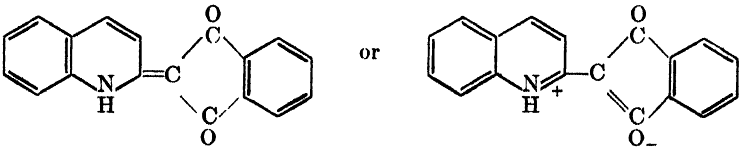


[a] The aldehyde is removed by steam distillation of the acyldihydroquinaldonitrile in 5 to 10 N sulfuric acid.

Quinoline Dyes.—*Quinoline yellow* (m.p. 234 to 235°) is a dyestuff, now obsolete, that is formed when quinaldine is heated with phthalic anhydride and zinc chloride.[150] The yellow dioxane solution gives a dark-red, a dark-orange, and an orange-yellow precipitate when treated with lithium, sodium, or potassium methoxide, respectively. The potassium derivative, treated with methyl sulfate, gives an N-methyl derivative, which gives no color with sodium methoxide and is degraded by oxidation with nitric acid to N-methyl-α-quinolone. These facts are in accordance with the assumption[151] that a zwitter ion is present.

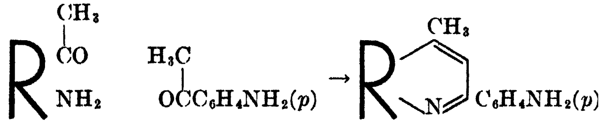
---

[147] Späth and Pikl, *Monatsh.*, **55**, 352 (1930).
[148] Spath and Brunner, *Ber.*, **57**, 1243 (1924).
[149] Grosheintz and Fischer, *J. Am. Chem. Soc.*, **63**, 2021 (1941).
[150] Eibner and Merkel, *Ber.*, **37**, 3006 (1906).
[151] Kuhn and Bär, *Ann.*, **516**, 155 (1935).



Flavaniline[152] is a dyestuff prepared by dehydration of acetanilide with zinc chloride or with excess acetic anhydride. The reaction proceeds in two stages: first the rearrangement of the N-acyl group, and second the condensation of the products to form the dye. The compound has since been displaced by better dyes.

$C_6H_5NHC(O)CH_3 \rightarrow o\text{-}H_2NC_6H_4C(O)CH_3 + p\text{-}H_2NC_6H_4C(O)CH_3$



The cyanine dyes[153] confer extra sensitiveness on silver halide photographic plates. Films that are ordinarily sensitive to the violet and blue region only of the spectrum become sensitive to the green, yellow, orange, red, and infrared when made or treated with the dye. Although this class of dyes was known in 1860, the application as photographic sensitizers was not known until 1928. The compounds owe their color[154] to a chain of alternating single and double bonds by virtue of which there is resonance caused by one equivalent of acid for two equivalents of the nitrogen atoms in the dye.

The dyes[155] consist of a quinoline ring with a tertiary nitrogen, joined directly or through carbon atoms, to another quinoline ring with a quaternary nitrogen. The simplest class, known as the *apocyanines*, contains no methenyl group between the two rings. They are prepared by boiling a concentrated methyl alcoholic solution of a quinolyl alkyl halide with caustic potash. Hydrochloric acid is eliminated; two isomeric dyes are formed. The formula of either dye can be written with two sequences of alternating single or double bonds either of which satisfy the valence requirements. Resonance exists.

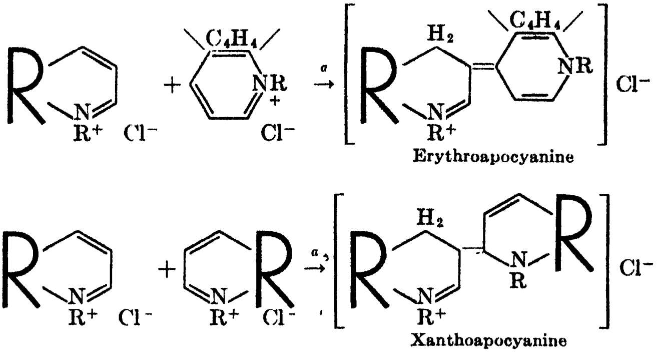
---

[152] (*a*) FISCHER and RUDOLPH, *Ber.*, **15**, 1500 (1882); (*b*) BESTHORN and FISCHER, *ibid.*, **16**, 68 (1883).

[153] MILLS and ORDISH, *J. Chem. Soc.*, **81** (1928); *cf.*, *Ann. Repts.*, **25**, 180 (1928).

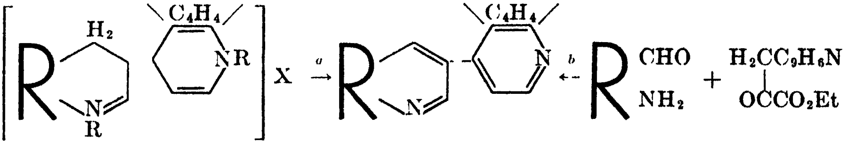
[154] BROOKER, *Rev. of Modern Phys.*, **14**, 275 (1942).

[155] DOJA, *Chem. Rev.*, **11**, 273 (1932).



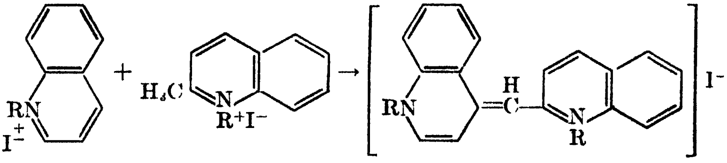
[a] KOH.

The erythro (red) isomer has more color because there are more double bonds between the two nitrogen atoms than are found in the xantho (Greek word for yellow) isomer. The structure of these compounds is shown by their degradation to a known diquinolyl



[a] Oxidation by I_2 or by dilute $KMnO_4$ in order to form the diammonium salt. Heat in vacuum in order to eliminate 2RI. [b] Friedländer's synthesis between o-aminobenzaldehyde and 4-quinolylypyruvate, which is prepared from lepidine, ethyl oxalate, and potassium methoxide. Hydrolysis and decarboxylation completes the formation of the diquinolyl.

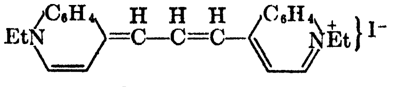
Cyanine dyes with one carbon atom between the two rings are prepared by a similar reaction between quinaldine ethiodide and quinoline ethiodide.



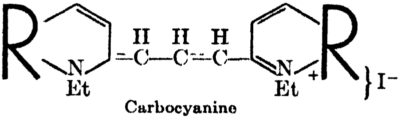
Isocyanine

A corresponding reaction with lepidine yields cyanine. The structure of these compounds is also shown by oxidation with permanganate. For example, isocyanine splits to the methosalt of cinchonic acid and to 1-methyl-2-quinolone.

Two quinoline rings with reactive methyl groups may be linked together with formaldehyde when their ethiodides are treated with sodium ethoxide. *Cryptocyanine,* a purple-black dye, whose sensitizing action extends far out into the red, and *carbocyanine,* the well-known commercial *pinacyanole*, are made in this manner from lepidine and quinaldine ethiodides, respectively.



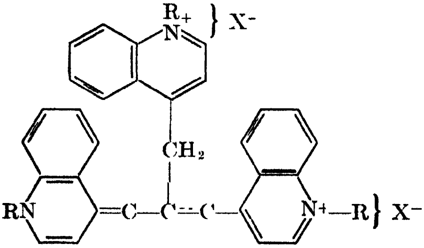
Cryptocyanine



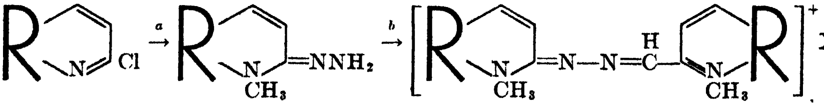
Carbocyanine

Large R = C_6H_4.

When lepidine alkyl *p*-toluenesulfonate is condensed with orthoformic ester in a small amount of pyridine, and the salt is converted to the bromide by sodium bromide, the product is *neocyanine*.



The preparation of cyanine dyes that have nitrogen instead of carbon links between the two quinoline nuclei is illustrated by the reaction between 1-methyl-2-quinolonehydrazone and quinoline-2-aldehyde methoperchlorate.[156]

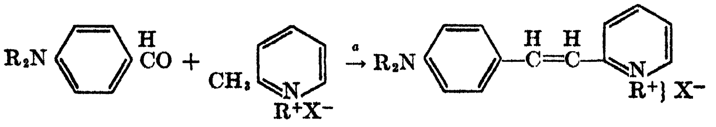


[a] The starting material is obtained from carbostyril and phosphorus oxychloride at 130 to 140°. The chloro product is treated successively with CH_3I at 80° for 30 hr., $H_2NNHCO_2CH_3$ in hot alcohol, hot HCl.

[b] The hydrazone is treated with N-methylquinaldinium perchlorate, which is made from the dimethyl sulfate addition product of *p*-nitrosodimethylaminobenzaldehyde and sodium perchlorate in the presence of piperidine. Hydrolysis with dilute acid gives the colored salt.

Similar dyes are prepared from other heterocyclic nuclei (see benzothiazole, Chap. XIV).

Dimethylaminobenzaldehyde has earlier been observed to condense readily with active methylene groups and yield colored salts. The styril compounds produced from the reaction of this aldehyde with the quaternary salts of pyridine and quinoline are also photographic sensitizers.[157]



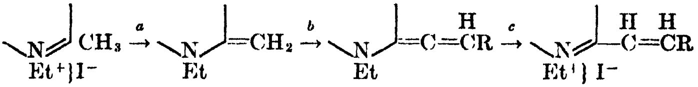
[a] Piperidine as a condensing agent.

---

[156] Fuchs and Grauaug, *Ber.*, **61**, 57 (1928).

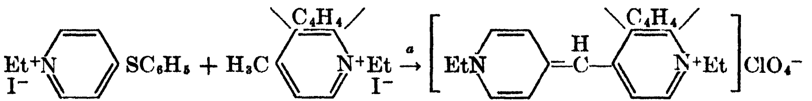
[157] Mills and Raper, *J. Chem. Soc.*, **127**, 2466 (1925).

The first step in this process is the formation of the active methylene base, which then condenses with the aldehyde to form the allene compound, which in turn adds hydriodic acid. These steps are shown clearly in partial formulas below for a molecule large enough to retard the changes to the point where the steps can be isolated readily.



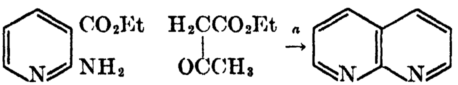
The quinoline system is benzo[*f*]quinoline, *i.e.*, 5,6-benzoquinoline.
R = *p*-dimethylaminophenyl.
[a] NaOH with air. [b] Dimethylaminobenzaldehyde. [c] Piperidine hydrochloride.

A further illustration of the variety of dyes in this class is found in the product of the condensation of 4-chloro- or 4-phenyl-mercaptopyridine ethiodide with lepidine ethiodide in the presence of triethylamine at 100° to give a 1,1′-diethyl-4-pyrido-4′-cyanine salt.[158]



[a] Et_3N. The thio ether was obtained from 4-chloropyridine and phenylmercaptan followed by treatment with ethyl iodide. The dye was precipitated as the perchlorate.

Naphthyridine.—The di-nitrogen heterologue[159] of naphthalene is called naphthyridine. It is prepared from a pyridine compound by methods that are entirely similar to those used in preparing quinoline. The sequence of reactions shown below illustrates the parallel nature of the changes.



[a] NaOH in abs. alc. at 140 to 150° for 7.5 hr., aq. KOH, HCl, PCl_5.

Problems

1. What is the product that results from the reaction of the following? (*a*) The monoanilide of malonic acid and phosphorus pentachloride.[15] (*b*) Aniline, sulfuric acid, sodium *m*-nitrobenzenesulfonate and a 2-alkyl-1,3-diethylglyceryl ether heated together for 24 hr. at 130 to 135°.[160] (*c*) 2-Aminobenzaldehyde and metazonic acid, $C_2H_4N_2O_3$ (metazonic acid is the oxime of nitroacetaldehyde which is prepared from 2 molecules of nitromethane and caustic alkali, and which exists in the equilibrium form $O_2NCH_2CH{=}NOH \rightleftarrows HOON{=}CH{-}CH{=}NOH$), followed by treatment of the product with stannous chloride and hydrochloric acid.[84] (*d*) Ethoxyacetonitrile (how prepared?) with methylmagnesium halide, and the product of this reaction

---

[158] Sprague and Brooker, *J. Am. Chem. Soc.*, **59**, 2697 (1937); Brooker *et al.*, *ibid.*, **62**, 1116 (1940).

[159] Koller and Strang, *Monatsch.*, **50**, 144 (1929).

[160] Darzens and Meyer, *Compt. rend.*, **198**, 1428 (1934); *C.A.*, **28**, 4422 (1934).

treated with isatin in the presence of 33 per cent alcoholic caustic.[161] (*e*) Arsanilic acid and benzaldehyde refluxed together in absolute alcohol until the acid is dissolved and the solution then treated with pyruvic acid.[125] (*f*) Ethyl acetonedicarboxylate, $OC(CH_2COOC_2H_5)_2$, and aniline at 100° followed by treatment with concentrated sulfuric acid.[162] (*g*) *o*-Aminobenzaldehyde and oximinoacetone, $CH_3COCH{=}NOH$, with 40 per cent potassium hydroxide.[122] (*h*) *o*-Aminoacetophenone boiled with formic acid.[163] (*i*) Anthranilic acid and furfural.[164] (*j*) N-Benzenesulfonylanthranilic acid boiled with acetic anhydride.[165] (*k*) *o*-Toluidine, glyoxal, and caustic soda at 150°.[166] (*l*) 6-Methoxyindole warmed with chloroform and sodium ethoxide.[167] (*m*) α-Nitronaphthalene, naphthylamine sulfate, glycerol, and concentrated sulfuric acid heated together until reaction begins (150 to 160°) and finally refluxed together.[168] (*n*) *o*-Chlorohydrocinnamic acid heated with copper and ammonia.[30]

2. The following questions are based on analogies with the reaction of pyridine compounds. What is the product formed from the following? (*a*) N-Propyltetrahydroquinoline and cyanogen bromide.[169] (*b*) Quinoline and methyl acetylenedicarboxylate.[170] (*c*) The iodomethylate of 6-acetylaminoquinoline treated with caustic alkali and then with potassium ferricyanide.[171] (*d*) 3-Bromoquinoline with *n*-butyllithium.[172] (*e*) Quinoline-2,3,5,6-tetracarboxylic acid refluxed in acetic acid.[71] (*f*) Quinoline with butyllithium.[173] (*g*) N-Benzoyltetrahydroquinoline and phosphorus pentachloride followed in turn by aqueous acid, nitrous acid, and alkali with zinc chloride.[174] (*h*) 2,4-Dimethylquinoline ethiodide 2-iodoquinoline ethiodide and triethylamine.[175a] (*i*) The N-oxide of 6-methoxyquinoline (how prepared?) with phosphorus oxychloride and the product of this reaction treated with 1-diethylamino-4-aminopentane.[175b]

3. What is the product obtained from each of the following reactions? (*a*) 2,3,8-Trimethylquinoline refluxed with selenium dioxide in ethanol.[123] (*b*) 2-Aldehydoquinoline with acetophenone and 10 per cent sodium hydroxide solution.[79]

4. The product of the action of metallic sodium on quinoline is 3,2′-diquinolyl. How would you prove the constitution of the product?[176]

5. What is the carbinol that forms when quinaldine is heated at 140° (oil bath temperature) with either ethyl oxomalonate, ethyl benzoylglyoxylate, or diphenyl triketone? How would each of the intermediates be prepared?[177]

---

[161] Cross and Henze, *J. Am. Chem. Soc.*, **61**, 2730 (1939).

[162] Besthorn and Garben, *Ber.*, **33**, 3439 (1900).

[163] Bischler and Burkart, *Ber.*, **26**, 1352 (1893).

[164] Ekeley and Rogers, *J. Am. Chem. Soc.*, **44**, 2655 (1922).

[165] Anschütz and Schmidt, *Ber.*, **35**, 3473 (1902); Heller and Grundmann, *ibid.*, **56**, 200 (1923).

[166] Kulisch, *Chem. Zeit.*, **27**, 279 (1903).

[167] Kermack, Perkin, and Robinson, *J. Chem. Soc.*, **121**, 1882 (1922).

[168] Skraup, *Monatsh.*, **2**, 162 (1881).

[169] v. Braun, *Ber.*, **42**, 2219 (1909).

[170] Diels and Alder, *Ann.*, **510**, 87 (1934).

[171] Decker and Kaufmann, *J. prakt. Chem.* [2], **84**, 442 (1911).

[172] Gilman and Spatz, *J. Am. Chem. Soc.*, **62**, 446 (1940).

[173] Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).

[174] v. Braun, *Ber.*, **43**, 2837 (1910).

[175a] Brooker and Smith, *J. Am. Chem. Soc.*, **59**, 67 (1937); *b.* Magidson and Rubstov, *J. Gen. Chem.* (U.S.S.R.), **7**, 1896 (1937); *C.A.*, **32**, 564 (1938).

[176] Weidel, *Monatsh.*, **2**, 491 (1881); Carlin and Einhorn, *Ber.*, **23**, 2895 (1890).

[177] McElvain and Johnson, *J. Am. Chem. Soc.*, **63**, 2213 (1941).

6. Ethyl acetonedicarboxylate, which is obtained easily from citronenic acid, is allowed to stand with anthranilaldehyde in alcohol with a small amount of potassium hydroxide for 10 days. What is the product formed?[178]

7. Ethyl anthranilate is condensed with ethyl malonate at 140 to 150° for 13 hr. in the presence of sodium alkoxide. The product is then heated with alcoholic ammonia for 10 hr. in an iron tube, and the new product is heated with phosphorus oxychloride for 24 hr. on a water bath to give a material with the composition $C_{10}H_4N_2Cl_2$. What is the compound probably formed?[179]

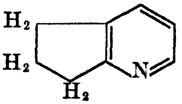
8. Benzoylacetonitrile is allowed to stand overnight in benzene with sodium sand, is treated with *o*-nitrobenzoyl chloride, and the product is then boiled with red phosphorus and hydroiodic acid for 30 min. What product is formed?[180]

9. A mixture of ethyl acetoacetate and *o*-toluidine is boiled together rapidly for about 1½ min. The crystals are then isolated, dissolved in concentrated sulfuric acid, and the solution heated on a water bath for 15 min. The product is then distilled with zinc dust. What is the final product of these changes?[181]

10. What is the product obtained in each step of the following sequence of reactions? (*a*) A mixture of acetophenone and paraldehyde is saturated with gaseous hydrochloric acid while being cooled with cold water and is then allowed to stand for 2 days. (*b*) The above mixture is shaken with *p*-anisidine, nitrobenzene, and concentrated hydrochloric acid and finally heated for 4 hr. on a water bath.[182]

11. What are the products obtained from the following two sequences[183] of reactions, each of which starts with 5-aminoquinoline (how prepared?) and progresses by b_1 or b_2, respectively? (*a*) Sodium nitrite followed by potassium arsenite. (b_1) The product from (*a*) treated with sodium hypophosphite and potassium iodide or (b_2) the product from (*a*) treated with potassium iodide, sulfuric acid, and sulfur dioxide followed by treatment with hydrochloric acid.

12. Suggest methods for the preparation of the following: (*a*) β-(2-quinolyl)acrylic acid.[184] (*b*) Quinolyl-4-pyruvic acid and -4-acetic acid[185] from homologues of quinoline.

13. 5,6-Dihydropyrindene  has been found as one of the compounds present in shale oil. Suggest a sequence of reactions for the preparation of this material from a nonheterocyclic source such as cyclopentanone.[186]

14. Describe a sequence of reactions for the preparation of δ-phenylbutylamine from a quinoline compound.[187]

15. Suggest a method for the preparation of each of the following quinoline compounds: (*a*) 2,4-Dimethyl-6-ethylquinoline.[188] (*b*) 5-Benzyl-8-hydroxyquino-

[178] Koller, Ruppersberg, and Strang, *Monatsh.*, **52**, 59 (1929).

[179] Koller, *Ber.*, **60**, 1108 (1927); Koller, Ruffersberg, and Strang, *Monatsh.*, **52**, 59 (1929).

[180] Gabriel and Gerhard, *Ber.*, **54**, 1616 (1921).

[181] Ewins and King, *J. Chem. Soc.*, **103**, 104 (1913).

[182] Koenigs and Jaeglé, *Ber.*, **28**, 1046 (1895).

[183] Binz and Rath, *Ann.*, **453**, 238 (1927).

[184] Einhorn, *Ber.*, **18**, 3465 (1885); Alberts and Bachman, *J. Am. Chem. Soc.*, **57**, 1284 (1935).

[185] Borsche and Bütschli, *Ann.*, **529**, 266 (1937).

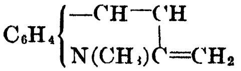
[186] Thompson, *J. Am. Chem. Soc.*, **53**, 3160 (1931).

[187] v. Braun, *Ber.*, **43**, 2837 (1910).

[188] Glenn and Bailey, *J. Am. Chem. Soc.*, **63**, 641 (1941).

line.[189] (*c*) 2(2′-Phenylquinolyl-4′)-quinoline-4-carboxylic acid.[129] (*d*) 2,2′-Phenyl-4,4′-carboxy-6,6′-arsenoquinoline by a sequence of reactions that starts with isatin.[190] (*e*) 6-Carboxy-2-phenylquinoline.[129] (*f*) α-(Tetrahydro-4-thiopyranyl)-γ-(4′-quinolyl)propane.[131] (*g*) 6′-Methoxy-9-rubanol.[191] (*h*) 8-δ-aminobutylamino-6-methoxyquinoline.[192] (*i*) 4 (*p*-hydroxyphenyl)-quinoline.[193] (*j*) *p*(6′Methoxy-2′-methyl-4′-quinolylamino)-phenylarsinic acid, $CH_3O,C_9H_4N \cdot (CH_3)NHC_6H_4AsO(OH)_2$.[194]

16. Benzotrichloride and 1-methyl-2-methylene-1,2-dihydroquinoline



$$C_6H_4\begin{cases}—CH—CH \\ N(CH_3)C{=}CH_2\end{cases}$$

yield a product that forms metallic green crystals from alcohol, dissolves in alcohol with a blue-violet color, and has the analysis N = 6.57 per cent, C = 79.96 per cent, and H = 5.83 per cent. What possibilities with respect to the structure of the product are present?[195]

17. What is the product obtained when quinaldine methiodide, ethyl orthoformate, and dry pyridine are refluxed together for 3 hr.?[196]

18. Nitration of 2,3,8-trimethylquinoline yields a nitro compound which by standard reactions is converted to a methoxy compound. It is desired to prove that the methoxy group is in the 5-position. Show a sequence of reactions for the preparation of this compound from such starting materials as toluene, acetaldehyde, and propionaldehyde.[123]

19. The simpler carbohydrates, including pentoses, decompose when distilled with sodium bicarbonate. One of the products is acetol, $CH_3C(O)CH_2OH$. The product is identified by heating *o*-amino-benzaldehyde with a few cubic centimeters of potassium hydroxide solution and noting the intense bluish-green fluorescence that results in sodium bicarbonate solution. What is the product that is formed in the test?[197]

20. What experimental conditions must be employed in order to obtain either 8-chloro-4-hydroxyquinaldine or 8-chloro-2-hydroxylepidine from reagents that are the same in each case?[198]

21. β-Collidine (4-methyl-3-ethylpyridine) is treated with a sequence of reagents ($CCl_3CHO + ZnCl_2$, NaOEt, $H_2 + PtO_2$, EtOH + HCl, C_6H_5COCl) to give $C_{17}H_{23}O_3N$. This compound in turn yields $C_{20}H_{26}N_2O_2$ when treated with another sequence of reagents (ethyl 6-methoxyquinate, $C_{18}H_{13}O_3$, and NaOEt; aqueous alkali followed by acid, heat, NaOBr, NaOEt, H_2 + Pd). What is the structure of the product finally obtained?[199]

---

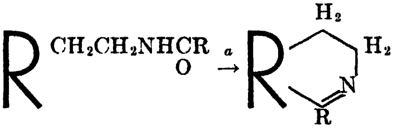
[189] McMaster and Bruner, *ibid.*, **57**, 1697 (1935).
[190] Calvery, Noller, and Adams, *J. Am. Chem. Soc.*, **47**, 3058 (1925).
[191] Prelog, Seiwerth, Heimbach-Jahasz, and Stern, *Ber.*, **74**, 647 (1941).
[192] Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).
[193] Besthorn and Jaeglé, *Ber.*, **27**, 907 (1894).
[194] Slater, *J. Chem. Soc.*, 1209 (1930).
[195] Fischer and Rosenhauer, *Z. angew. Chem.*, **36**, 330 (1923).
[196] Hamer, *J. Chem. Soc.*, 2796 (1927).
[197] Baudisch and Deuel, *J. Am. Chem. Soc.*, **44**, 1585 (1922).
[198] Krahler and Burger, *ibid.*, **64**, 2417 (1942).
[199] Rabe, Huntenberg, Schultze, and Volger, *Ber.*, **64**, 2487 (1931).

CHAPTER XI

ISOQUINOLINES

Isoquinoline is found with quinoline in coal tar,[1] and the isoquinoline system is widely distributed in nature among the alkaloids. In the laboratory, these heterocyclic compounds are made by methods that are quite different from those used for the preparation of quinoline because of the difference in the position of nitrogen. The chemical reactions are, however, very similar, since both are benz-substituted pyridines.

Methods of Preparation.—Four types of intermediates are used in the synthesis. By far the most common is a β-aminoalkylbenzene which (*a*) by means of its acyl or aroyl derivative, (*b*) by use of an aldehyde, or (*c*) by employment of an arylethylglycine derivative can be caused to condense to an isoquinoline. The reaction with the acyl or aroyl derivative is known as the *Bischler and Napieralski*[2] *reaction*, since much improved by the work of Pictet[3] and of Decker.[4] It leads to a dihydro product, which is readily oxidized by mild reagents to an isoquinoline.



[a] P_2O_5, PCl_5, $POCl_3$, $AlCl_3$, $ZnCl_2$, or $FeCl_3$ in boiling benzene or toluene.

If the acyl derivative of a secondary amine is used, an ammonium salt must participate in formation of the ring, and the product becomes a quaternary salt. If there is an active hydrogen atom on the carbon next to the carbonyl group, ring closure may involve formation of the double bond outside the ring. Both modifications are shown below in *A* and *B*, respectively, by partial formulas that indicate the pertinent changes in the reagent and product.

---

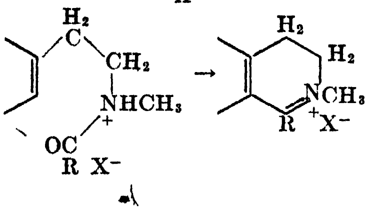
[1] Hoogewerff and van Dorp, *Rec. trav. chim.*, **4**, 125 (1885).

[2] Bischler and Napieralski, *Ber.*, **26**, 1903 (1893); *cf.* Manshe, *Chem. Rev.*, **30**, 145 (1942).

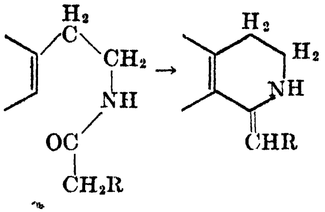
[3] Pictet and Kay, *Ber.*, **42**, 1973 (1909); Pictet and Finkelstein, *ibid.*, 1979; Pictet and Gams, *ibid.*, **43**, 2384 (1910)..

[4] Decker and Kropp, *ibid.*, **42**, 2075 (1909); Decker, Kropp, Hoyer, and Becker, *Ann.*, **395**, 299 (1913).

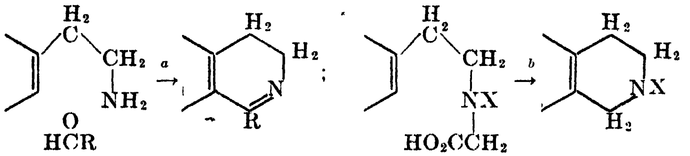
A



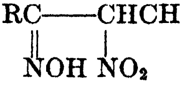
B



β-Aminoalkylbenzene[5] condenses also with aldehydes and forms tetrahydro products which likewise are oxidized readily to an isoquinoline derivative. This method has considerable value as a possible biological synthesis,[6] since the reaction takes place at ordinary temperatures and is sensitive to the pH of the medium. Acetaldehyde, for example, condenses in good yield with 3,4-dihydroxyphenyl ethyl amine at pH = 5, when the mixture is allowed to stand at 25° for 72 hr. A third way[7] in which β-aminoalkylbenzenes can be used shows the great tendency of the isoquinoline nucleus to form even when a seven-membered ring might be expected. These last two modifications are likewise shown, respectively, by partial formulas below in which the essential changes only in reagent and product are indicated.



[a] Allowed to stand in a solution at a definite pH value. [b] PCl_5 to form the acid chloride, $AlCl_3$ to effect ring closure with simultaneous loss of HCl and CO_2. $X = C_6H_5SO_2$.

Methods for the preparation of the all-important β-aminoalkylbenzenes are listed in Table I. The majority of the processes are conventional. The reduction of an oxime, as in examples 1 and 2, is very common. The formation of an isonitroso compound from a ketone (example 3) has been met before in the synthesis of pyrroles. The reduction of nitriles (example 4) is one of the most frequently used methods for preparing amines. The preparation of nitrosites as in example 5 is interesting because of the considerable study on the question of the structure of these compounds which have both a nitroso group, capable of isomerizing readily to an oxime,  $\underset{\text{NOH}}{\underset{\|}{RC}}\text{——}\underset{NO_2}{\underset{|}{CHCH_3}}$, and a nitro group. When the propanol amine product of this sequence is converted to isoquinoline, water is simultaneously eliminated, so that a double bond at the 3,4-position is formed. The azide used in example 6 is made from the acid chloride and sodium azide or from the ester and hydrazine followed by nitrous acid.

---

[5] Pictet and Spengler, *Ber.*, **40**, 2030 (1911).

[6] Schopf and Bayerle, *Ann.*, **513**, 190 (1934).

[7] v. Braun and Wirz, *Ber.*, **60**, 102 (1927).

When the amine is prepared by a Beckmann rearrangement as under *B* in Table I, the process may proceed without interruption to an isoquinoline derivative, particularly if a ketoxime is employed. This result is caused, of course, by the fact that the products of the rearrangement are an amine and an acid chloride, which unite to form an amide, which in turn undergoes the conventional Bischler and Napieralski synthesis.

Under *C* are listed a number of preparations in which the nitrogen atom is substituted with the group necessary for ring closure. For example, the hippuric acid in example 11 already has the benzoyl substituent attached to nitrogen. The necessary chain length is acquired by condensation of the acid with an aldehyde. Decomposition of the azide as in example 12 leads to an isocyanate which requires only the addition of hydrogen chloride to be a formamide, which is suitable for ring closure to an isoquinoline.

TABLE I.—METHODS FOR THE PREPARATION OF β-ARYLETHYLAMINES, THEIR ACETYL OR AROYL DERIVATIVE OR RELATED COMPOUNDS, IN ORDER TO USE THEM FOR THE SYNTHESIS OF ISOQUINOLINE COMPOUNDS

R = an aryl nucleus

A. By reduction primarily.

1. $RCH_2CHO \xrightarrow{a} RCH_2CH{=}NOH \xrightarrow{b} RCH_2CH_2NH_2$

[a] H_2NOH. [b] NaHg[2].

2. $RCHO \xrightarrow{a} RCH{=}CHNO_2 \xrightarrow{b} RCH_2CH{=}NOH \xrightarrow{c} RCH_2CH_2NH_2$

[a] CH_3NO_2, + alc. KOH. [b] AlHg or Zn dust + HOAc. [c] NaHg + HOAc.[8]

3. $RC(O)CH_3 \xrightarrow{a} RC(O)CH{=}NOH \xrightarrow{b} RC(O)CH_2NH_2$

[a] HNO_2. [b] NaHg + HOAc.[9]

4. $RCH_2CN \xrightarrow{a} RCH_2CH_2NH_2$

[a] Zn + HCl, Na + abs. alc., or H_2 + Raney Ni.[10]

5. $RCH{=}CHCH_3 \xrightarrow{a} RCH(NO)CH(NO_2)CH_3 \xrightarrow{b} RCH(OH)CH(CH_3)NH_2\,]$

[a] $NaNO_2 + H_2SO_4$. [b] $Ac_2O + H_3PO_4$ to form the acetoxy nitro compound, electrolytic H_2 in acid solution.[11]

6. $RCH_2CH_2C(O)N_3 \xrightarrow{a} RCH_2CH_2NH_2$

[a] The azide is treated with Br_2 in dry $CHCl_3$ or is boiled in alc. The product is then treated with hot conc. HCl.[12]

B. By Hofmann reaction or Beckmann rearrangements with successive stages that sometimes lead to an isoquinoline compound without isolation of the amine.

7. $RCH_2CH_2C(O)NH_2 \xrightarrow{a} RCH_2CH_2NH_2$

[a] KOBr or NaOCl.[13]

TABLE I.—METHODS FOR THE PREPARATION OF β-ARYLETHYLAMINES, THEIR ACETYL OR AROYL DERIVATIVE OR RELATED COMPOUNDS, IN ORDER TO USE THEM FOR THE SYNTHESIS OF ISOQUINOLINE COMPOUNDS.—(*Continued*)

8. $RCH_2CH_2CHO \xrightarrow{a} RCH_2CH_2NH_2$

[a] H_2NOH, $POCl_3$, H_2O + alk.[14]

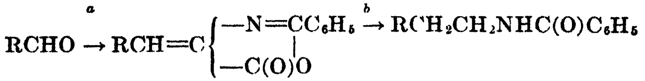
✓ 9. $RCH{=}CHC(O)CH_3 \xrightarrow{a} RCH{=}CHC(CH_3){=}NOH \xrightarrow{b}$ an isoquinoline

[a] H_2NOH. [b] $POCl_3$.[15]

10. $RCHO \xrightarrow{a} RCH{=}CHC(O)CH_3 \xrightarrow{b}$ an isoquinoline

[a] $CH_3C(O)CH_3$. [b] H_2 + PtO_2, H_2NOH, $POCl_3$.[16]

C. By preparation of an acetyl or aroyl amine or of an isocyanate, followed by ring closure.

11. 

$$RCHO \xrightarrow{a} RCH{=}C\begin{cases}—N{=}CC_6H_5\\—C(O)O\end{cases} \xrightarrow{b} RCH_2CH_2NHC(O)C_6H_5$$

[a] Hippuric acid. [b] Esterification and catalytic reduction of the azlactone.[17]

12. $RCH_2CH_2CO_2Et \xrightarrow{a} RCH_2CH_2C(O)N_3 \xrightarrow{b}$ an isoquinoline

[a] H_2NNH_2, HNO_2. [b] Decomposition in boiling toluene, reaction of the isocyanate with $POCl_3$ at 110° for 2 hr.[18]

13. $RC(O)CH_3 \xrightarrow{a} RC(O)CH_2NH_2 \xrightarrow{b}$ an isoquinoline

[a] HNO_2, cat. H_2. [b] $R'CH_2COCl$, NaHg in abs. alc. at 60 to 70° causes reduction to a secondary alcohol, P_2O_5.[3]

[8] ROSENMUND, *ibid.*, **42**, 4778 (1909).

[9] BISCHLER and NAPIERALSKI, *Ber.*, **26**, 1903 (1893).

[10] BERNTHSEN, *Ann.*, **184**, 304 (1876); LADENBERG, *Ber.*, **19**, 782 (1886); JOHNSON and GUEST, *Am. Chem. J.*, **42**, 346 (1920); DECKER and BECKER, *Ber.*, **45**, 2405 (1912); MAILNE, *Bull. soc. chim.* [4], **23**, 232 (1918); ROBINSON JR. and SNYDER, *Org. Syntheses*, **23**, 71 (1943).

[11] BRUCKNER and KRÁMLI, *J. prakt. Chem.*, **145**, 291 (1936).

[12] CURTIUS and JORDAN, *ibid.*, [2], **64**, 297 (1901); CURTIUS and BOETZELEN, *ibid.*, 314.

[13] WEERMAN and JONGKEES, *trav. chim.*, **25**, 242 (1906); see also ref. 3.

[14] v. BRAUN and KRUBER, *Ber.*, **45**, 384 (1912).

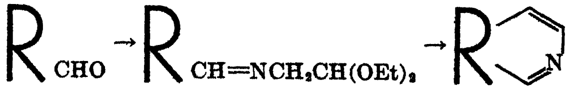
[15] ZELINSKY, *ibid.*, **20**, 922 (1887); BURSTIN, *Monatsh.*, **34**, 1443 (1913).

[16] SUGASAWA and YOSHIKAWA, *J. Chem. Soc.*, 1583 (1933); see also Ref. 3.

[17] ERLENMEYER, *Ann.*, **337**, 265 (1904); HARTMAN and KAGI, U.S. patent 1,437,802 (1922); *C.A.*, **17**, 854 (1923).

[18] MOHUNTA and RAY, *J. Chem. Soc.*, 1263 (1934).

✓The second class of compounds, besides the β-phenylethylamines, which can be used as major starting materials for synthesis of isoquinoline compounds, consists of aromatic aldehydes. These reagents condense readily with aminoacetals, and the products, such as $C_6H_5CH{=}NCH_2CH(OEt)_2$, readily undergo ring closure with strong sulfuric acid or dehydrating agents to form isoquinolines.[19]



Ring closure apparently will not occur unless the reagent has a system of

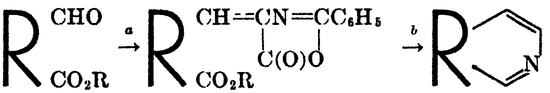
[19] POMERANZ, *Monatsh.*, **14**, 116 (1893); **15**, 300 (1894); **18**, 1 (1897).

conjugated double bonds, $C_6H_5C{=}NCH{=}CHOR$, or is capable of forming such a system during the reaction.[20]

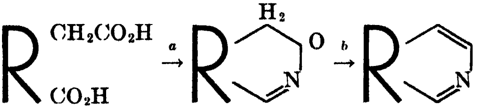
The third general type of intermediate includes the *o*-substituted benzoic acids or related compounds such as nitriles. These intermediates are readily convertible to amides which can then undergo condensation with certain *o*-substituents. The reactions listed in Table II show how appropriate groups have been obtained for preparations by this general method.

TABLE II.—SYNTHESIS FROM DIORTHOSUBSTITUTED INTERMEDIATES THAT WILL READILY UNDERGO CONDENSATION TO ISOQUINOLINE COMPOUNDS

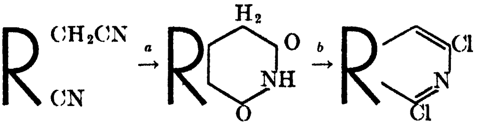
Ref.

1.  21

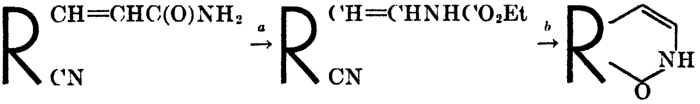
[a] Hippuric acid with acetic anhydride. [b] Hydrolysis of the azlactone and the ester, decarboxylation, $POCl_3$, HI + red P at 150–170°.

2.  22

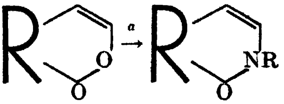
[a] NH_3. [b] $POCl_3$, HI, or Zn dust. This synthesis, in which HI is used, was employed for the first preparation of isoquinoline.

3.  23

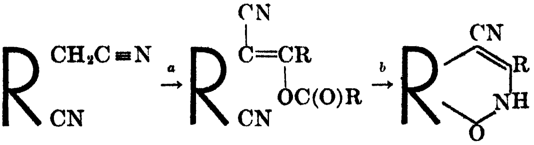
[a] H_2SO_4. [b] $POCl_3$.

4.  24

[a] NaOCl in CH_3OH. [b] HCl.

5.  25

[a] RNH_2.

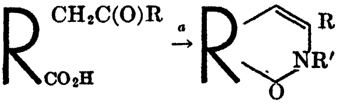
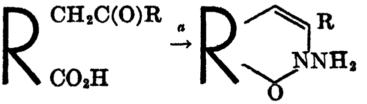
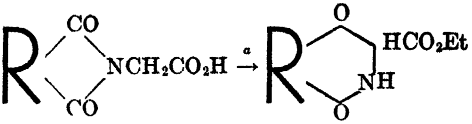
6.  26

[a] $(RCO)_2O$, for example acetic anhydride. [b] Alkali hydrolyses the acetyl group and simultaneously hydrolyses the aromatic nitrile group to an amide that undergoes ring closure.

---

[20] STAUB, *Helv. Chim. Acta*, 5, 888 (1922).

Table II.—Synthesis from Diorthosubstituted Intermediates That Will Readily Undergo Condensation to Isoquinoline Compounds.—(*Continued*)

7.	 ^{a} $R'NH_2$.	27
8.	 ^{a} H_2NNH_2.	28
9.	 ^{a} NaOEt at 100°.	29

[21] Bain, Perkin, and Robinson, *J. Chem. Soc.*, **105**, 2392 (1914); Gabriel and Colman, *Ber.*, **33**, 980 (1900).

[22] Gabriel, *ibid.*, **19**, 1653, 2354 (1886); Leblanc, *ibid.*, **21**, 2299 (1888).

[23] Gabriel, *ibid.*, **20**, 2499 (1887).

[24] Gabriel, *ibid.*, **49**, 1608 (1916).

[25] Gabriel, *ibid.*, **18**, 1251, 2433, 3470 (1885); **19**, 830, 1653 (1886).

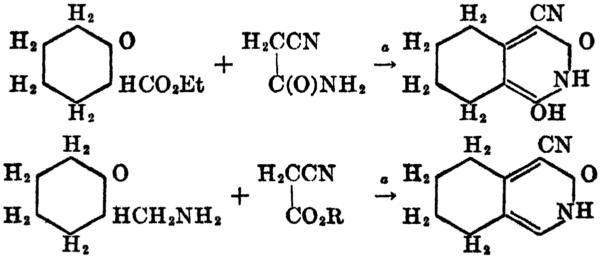
[26] Gabriel and Neumann, *ibid.*, **25**, 3563 (1892); Gabriel and Posner, *ibid.*, **27**, 827 (1894); Damerow, *ibid.*, **27**, 2232 (1894).

[27] Gabriel, *ibid.*, **18**, 2433 (1885); Heilman, *ibid.*, **23**, 3157 (1890) Fristsch, *ibid* **26**, 419 (1893).

[28] Gottlieb, *ibid.*, **32**, 958 (1899); Lieck, *ibid.*, **38**, 3853 (1905); Wölbling, *ibid.*, **38**, 3845 (1905).

[29] Gabriel and Colman, *ibid.*, **33**, 980, 2630 (1900); **35**, 2421 (1902).

Finally, isoquinoline compounds can be prepared from cyclohexanones[30] by methods somewhat analogous to those used in the pyridine series. For example, ethyl cyclohexanone-*o*-carboxylate condenses with a cyanoacetamide; or an amine, derived from the reduction product of ethyl cyclohexanone-*o*-carboxylate, condenses with ethyl cyanoacetate.



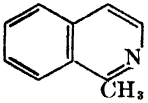
^{a} Na in benzene.

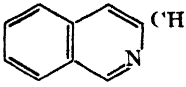
Reactions of Isoquinoline Compounds.—The reactions of isoquinoline are in general so similar to those of quinoline that only a few comments need be made. The problem[31] of the static bond (see page 391) in cyclic conjugated systems is of special interest because methyl groups can be placed on either side of the ring nitrogen atom as in 1-methyl- and 3-methyl-isoquinoline below. If the double bond is fixed, 1-methyl-, but not 3-methyl-isoquinoline, will condense with (*a*) dimethylamino-

---

[30] Basu, *J. Indian Chem.*, **8**, 319 (1931); Basu and Banerjee, *Ann.*, **518**, 243 (1935).

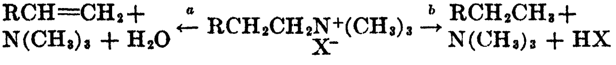
[31] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).





benzaldehyde, when heated with an alcoholic solution of piperidine, or (*b*) benzaldehyde with zinc chloride at 100°. If the double bond oscillates, both methyl groups will condense. In practice, only one benzylidene derivative, that from the 1-methyl-compound, is produced from each aldehyde. Presence of a benz substituent has apparently produced fixation of the bond or has so affected the resonance that only one of the methyl groups reacts.

The method by which the ring is opened when the completely methylated ammonium salt is degraded—the **exhaustive methylation process**—has received considerable attention in this series because it is used so often in the determination of the structure of alkaloids. The process consists essentially of methylation of the nitrogen atom as far as possible and then cleavage of a carbon-nitrogen link of the methylated ammonium compound. This last step may be accomplished by heat or reduction according to the general reactions shown by noncyclic compounds.



$$\begin{matrix} RCH{=}CH_2 + \\ N(CH_3)_3 + H_2O \end{matrix} \xleftarrow{a} RCH_2CH_2\underset{X^-}{N^+}(CH_3)_3 \xrightarrow{b} \begin{matrix} RCH_2CH_3 + \\ N(CH_3)_3 + HX \end{matrix}$$

[a] Ag_2O, ROH, NaOH, followed by heat. [b] NaHg, cat. H_2 or elec. H_2.

This decomposition of substituted ammonium hydroxides was discovered by Hofmann[32] and has been studied extensively because of its theoretical interest,[33] its use in the synthesis of olefins, and its application to the degradation of heterocyclic compounds that contain nitrogen. The noncyclic as well as cyclic systems have been subjected to this treatment. In general, if a completely alkylated ammonium salt is heated, a β-hydrogen on an alkyl group is eliminated with formation of an olefin, a tertiary amine, and water. The olefin will come principally from the ethyl radical (Hofmann's rule) if one is present (see Table III, equation 1). Elimination will be facilitated by the presence of a β-phenyl group (equation 2) and even more so by a nitrophenyl group. That is to say, a group that facilitates the ionization of carboxylic acid will likewise facilitate the extrusion of the hydrogen in this reaction. In the absence of an ethyl group, the shortest and least branched (at the beta position) alkyl radical is most apt to be separated as the olefin (equation 3). If branching at the beta-position is extensive, particularly if the branches are long alkyl chains (equation 4), the ease of elimination of the β-hydrogen atom is reduced and the process may produce methyl alcohol instead. An alkyl substituent at the alpha position, however, as in equation 5, has little effect. If no hydrogen atom is available in the beta position, the ammonium compound will probably split into a tertiary amine and an alcohol (equations 6 and 7).

---

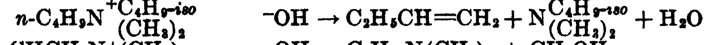
[32] Hofmann, *Ber.*, 14, 659 (1881); *Ann.*, 78, 253 (1851); 79, 12 (1851).

[33] Hankart and Ingold, *J. Chem. Soc.*, 997 (1927).

The temperature at which decomposition occurs depends on the ease with which the β-hydrogen atom is eliminated. This reaction may require relatively high temperatures (140 to 160°), may occur in boiling water, or, as in the case of a β-nitrophenylethyl methylated amine, may take place at a temperature so low that the ammonium salt is not isolated as an intermediate step.

The quaternary hydroxide is not the only type of ammonium compound that can decompose. The phenoxide yields 65 per cent anisole on decomposition (equation 8). This last form of splitting is favored as the strength of the anion increases. In fact, the elimination of methyl chloride from the chloride salt by heating at reduced pressure is one of the favorite methods for the obtention of the free base from ammonium compounds of high molecular weight. The manner in which the ammonium compounds decompose, therefore, is related in a general way to the strength of the anion and to the availability of the β-hydrogen atom. This last factor is, in turn, nicely interpreted by Ingold[33] and coworkers in terms of electron affinities and a hydrogen atom that is in a state of incipient ionization. Instances are not unknown, of course, where elimination of α- or γ-hydrogen atoms[34] occurs, but the β-hydrogen is usually the one removed.

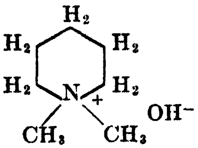
TABLE III.—GENERAL METHODS FOR DECOMPOSITION OF COMPLETELY METHYLATED AMMONIUM COMPOUNDS

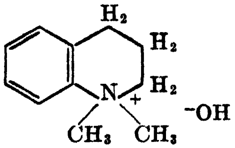
1. $C_2H_5N^+(CH_3)_2C_3H_7 \quad {}^-OH \rightarrow CH_2{=}CH_2 + C_3H_7N(CH_3)_2 + H_2O$
2. $C_6H_5CH_2CH_2N^+(CH_3)_3 \quad {}^-OH \rightarrow C_6H_5CH{=}CH_2 + N(CH_3)_3 + H_2O$
3. 
$n\text{-}C_4H_9N^{+C_4H_9\text{-}iso}_{(CH_3)_2} \quad {}^-OH \rightarrow C_2H_5CH{=}CH_2 + N^{C_4H_9\text{-}iso}_{(CH_3)_2} + H_2O$
4. $(n\text{-}C_3H_7)_2CHCH_2N^+(CH_3)_3 \quad {}^-OH \rightarrow C_8H_{17}N(CH_3)_2 + CH_3OH$
5. $CH_3CH(C_2H_5)N^+(CH_3)_3 \quad {}^-OH \rightarrow CH_2{=}CHC_2H_5 + N(CH_3)_3 + H_2O$
6. $C_6H_5CH_2N^+(CH_3)_3 \quad {}^-OH \rightarrow C_6H_5CH_2OH + N(CH_3)_3$
7. $C_6H_5N^+(CH_3)_3 \quad {}^-OH \rightarrow C_6H_5N(CH_3)_2 + CH_3OH$
8. $C_3H_7N^+(CH_3)_3 \quad {}^-OC_6H_5 \rightarrow C_3H_7N(CH_3)_2 + CH_3OC_6H_5$

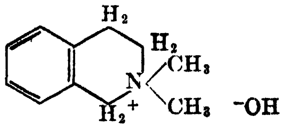
As applied to the problem of ring opening of a heterocyclic compound, it is obvious that piperidine, tetrahydroquinoline, and tetrahydroisoquinoline are but modifications of the general principles already discussed.

---

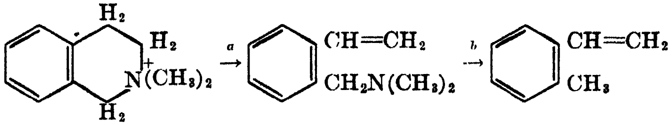
[34] INGOLD and ROGERS, *ibid.*, 722 (1935).





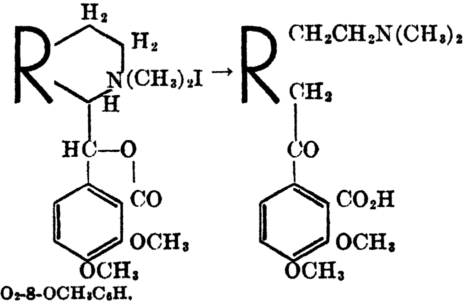


The piperidinium base has no labilizing group to activate the β-hydrogen atom. Hence it is the most difficult of the three to cleave. The tetrahydro quinoline salt is the next most difficult base to break, and the cleavage will, of course, occur between the 1- and 2-positions to give o-$(CH_3)_2NC_6H_9C_3H_7$[35] when sodium amalgam is used. The tetrahydroisoquinoline compound, on the other hand, has a phenyl group on the same carbon atom that loses the hydrogen. Hence it decomposes the most readily of all. The removal of nitrogen from this last compound is accomplished by a second treatment.



[a] NaHg. [b] CH_3I, AgCl, NaHg.

Occasionally, the elimination takes an unexpected course as in the case of narcotine methiodide.[36] The effect in this instance, however, merely means that the hydrogen atom, attached to the carbon in the lactone system, is more active than that which has only the influence of the substituted aromatic nucleus. In other words, there are two β-hydrogens that can be eliminated, and the more reactive one is in another ring.



Large R = 6,7-CH_2O_2-8-OCH_3C_6H.

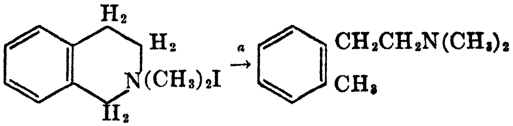
Reductive scission can be applied directly to the salts, in which case the hydroxide may be a possible intermediate, though the bonds broken are not always those cleaved thermally. Emde[37] heated a saturated aqueous solution of the ammonium salt with sodium amalgam. He also split[38] the salt by hydrogen over palladium-barium sulfate or platinic oxide in aqueous or acetic acid solution in the presence of sodium acetate. Electrolytic reduction[39] at a lead cathode is also an effective method. An application to a tetrahydroisoquinoline system in which the iodide salt is reduced over platinic oxide is shown below.

---

[35] Emde, *Ann.*, **391**, 88 (1912).

[36] Stevens, Creighton, Gordon, and MacNicol, *J. Chem. Soc.*, 3193 (1928).

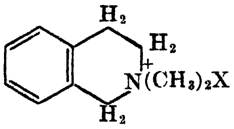
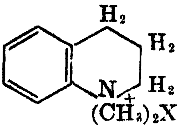
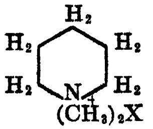
[37] Emde, *Helv. Chim. Acta*, **15**, 1330 (1932); *cf.* Ref. 35.



[a] H_2 over PtO_2 in H_2O.

Reagents do not, of course, react with equal ease, nor does a single reagent give the same result under all conditions. The above tetrahydroisoquinoline compound, for example, is not cleaved[38] in acetic acid solution by hydrogen over palladium-barium sulfate or platinic oxide. It is, however, attacked by 5 per cent sodium amalgam when the concentrated aqueous solution of its chloride or iodide salt is heated on a water bath. By contrast, the corresponding quinolinium chloride, but not the iodide, is attacked under the same conditions. The *o*-propyldimethylaniline, $C_3H_7C_6H_4N(CH_3)_2$, that forms can, in turn, be converted to the trimethylanilinium chloride and cleaved electrolytically

TABLE IV

Ammonium salt	Treated with hydrogen over			
	PtO₂ in		Pd-BaSO₄ in	
	Water	Acetic acid	Water	Acetic acid
	Iodide cleaved	Iodide not cleaved	....	Iodide not cleaved
	Either the chloride or iodide cleaved	Chloride and iodide resistant	Iodide not cleaved	Iodide not cleaved
	Neither the iodide nor chloride cleaved			

---

[38] EMDE and KULL, *Arch. Pharm.*, **274**, 173 (1936).

[39] EMMERT, *Ber.*, **42**, 1507, 1997 (1909); **45**, 430 (1912).

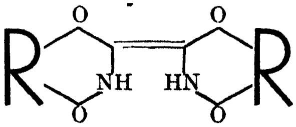
to trimethylamine and propylbenzene. Table IV shows the approximate decreasing order of strength of reagent from left to right and the increasing resistivity of the ammonium salt from top to bottom. The chloride salt is cleaved more readily than the iodide. The data are from the work of Emde and Kull.

SPECIAL COMPOUNDS

Isoquinoline melts at 23° and boils at 243°. Its preparation can be effected by the processes shown in Table I.

Isocarbostyril (α-hydroxyisoquinoline) is prepared from isocoumarin and alcoholic ammonia at 120 to 130° (equation 5, Table II). The product melts at 208° and exhibits in general the tautomeric behavior shown by carbostyril.[40]

1,4-Dihydroxyisoquinoline, prepared from phthalimide by the method already suggested (Table II, equation 9) is of some interest because it has the same grouping, —C(O)CH_2NH—, that is present in indoxyl. Hence it condenses with benzaldehyde or isatin and undergoes spontaneous oxidation in alkaline solution with hydrogen peroxide to a dyestuff known as carbindigo.[41]



The isoquinoline carboxylic acids are useful for identification and location of substituents (see Table V).

TABLE V

Position of Carboxyl Group	M.P., °C.
1[a]	161
3	272
4	264–266
5	280–282
6	355–360[b]
7	295–297
8	292–294[b]

[a] Common name is isoquinaldinic acid. [b] Melts with gradual darkening.

They are prepared by conventional methods. For example, isoquinaldinic acid[42] is obtained from a suspension of isoquinoline in an aqueous

---

[40] HARTLEY and DOBIE, *J. Chem. Soc.*, **75**, 640 (1899); FRIEDLÄNDER and MÜLLER, *Ber.*, **40**, 2009 (1887).

[41] GABRIEL and COLMAN, *ibid.*, **33**, 996 (1900); **35**, 2426 (1902); **38**, 579 (1903).

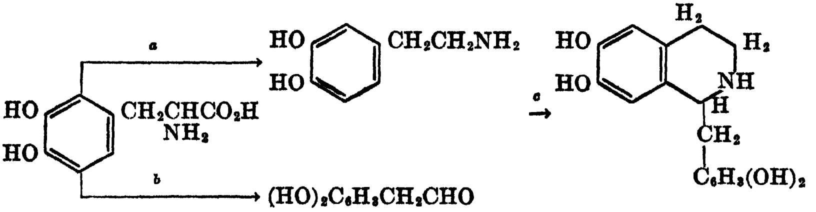
[42] REISSERT, *ibid.*, **38**, 3415 (1905); KAUFMANN and DÄNDLIKER, *ibid.*, **46**, 2929 (1913).

10 per cent potassium cyanide solution, which is treated with benzoyl chloride, followed by hydrolysis of the 1-cyano-2-benzoyl-1,2-dihydroisoquinoline product with 36 per cent hydrochloric acid in order to split the compound to benzaldehyde and isoquinaldinic acid. The process is similar in principle to the decomposition of acyl 1,2-dihydroquinaldonitriles mentioned in the preceding chapter as a method for the preparation of aldehydes. The 4-carboxylic acid is obtained as the product of a sequence of reactions in which the hydrobromide of isoquinoline dibromide is heated in an oil bath to 180 to 200°, the monobromo product is treated with cuprous cyanide,[43] and the resulting nitrile is then hydrolyzed with concentrated hydrochloric acid in a sealed tube at 150°.[44] The 5-,6-,7-, and 8-carboxylic acids are prepared by condensation of an appropriate bromobenzaldehyde with aminoacetal, followed by dehydration of the aminoacetal product with a mixture of sulfuric acid and phosphorus pentoxide and other conventional changes.

ISOQUINOLINE ALKALOIDS

The study of isoquinolines is closely related to the chemistry of the isoquinoline alkaloids. These compounds have been examined extensively, so that by now the biogenic origin appears reasonably well understood, the methods for degradation and synthesis are fairly standard, and the classification of various types (division into five groups will be employed in the text) is very complete. Particularly are these conditions true with the simpler members of the series.

These alkaloids are believed to be derived[45] from the amino acids of the tryptophan type which would be derived from the breakdown of proteins. Such acids undergo degradation: (*a*) by loss of carbon dioxide and (*b*) by loss of ammonia and carbon monoxide to give the necessary reactive units. The degradation products then combine.



[a] Loss of CO_2. [b] Loss of CO and NH_3. [c] Loss of H_2O.

The resulting benzylisoquinoline can then undergo further condensations through the phenolic groups or other reactive center in order to produce more condensed compounds. The remaining hydroxyl groups are frequently methylated.

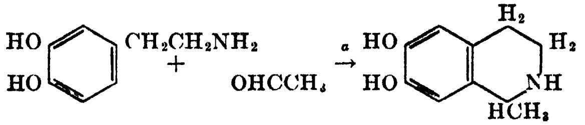
---

[43] Edinger and Bossung, *J. prakt. Chem.*, **43**, 192 (1891).

[44] Tyson, *J. Am. Chem. Soc.*, **61**, 183 (1939).

[45] Winterstein and Trier, "Die Alkaloids Bornträger," Berlin, 1910; Robinson, *J. Chem. Soc.*, 1083 (1936).

The simplicity with which these biogenic syntheses occur is seen by the preparation of norsalsoline in 85 per cent yield at a pH-5 and at 25°. The acetaldehyde can come from decomposition of alanine, $CH_3CH(NH_2)$-CO_2H, according to the above-mentioned plan.



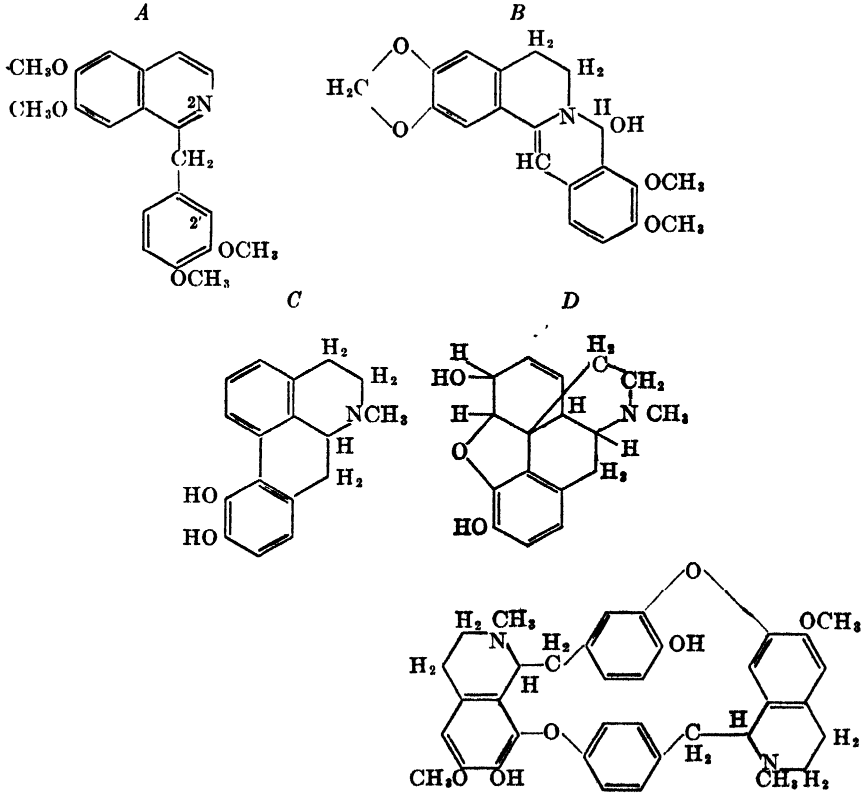
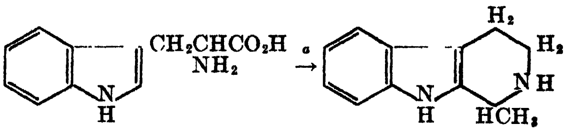


FIG. 1.—Types of alkaloids of the isoquinoline group.

By similar changes, tryptophan itself should form the ring system of the harmaline alkaloids (page 348)

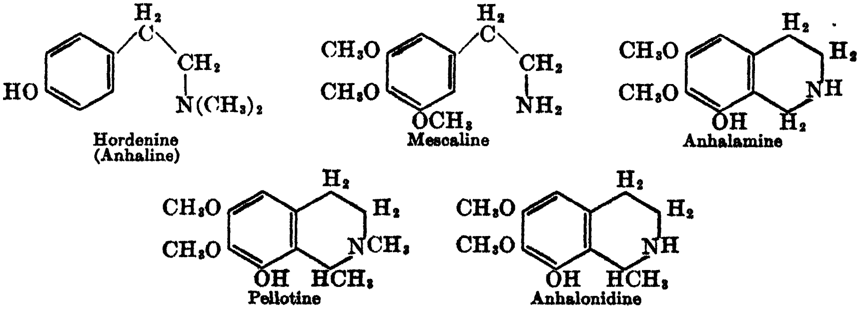


[a] Loss of CO_2, biogenic condensation with acetaldehyde.

The isoquinoline alkaloids can be classified into about five groups (see Fig. 1) depending on the complexity and degree of ring closure. Simplest of all are the substituted isoquinolines (*A*). In the opium group, this class is known as the papaverine type, and papaverine itself is represented in this illustration. When an appropriate substituent is present at the 2′-position so that ring closure can be effected with the nitrogen atom, the berberine type, represented by berberine (*B*), is produced. Ring closure with the other half of the isoquinoline nucleus yields the phenathripyridine type, represented by apomorphine (*C*). The morphine type, as represented by morphine (*D*), is a more complicated form that changes to apomorphine when heated with acid. The type shown in *E* is a bisisoquinoline.

The cactus alkaloids contain the simplest type only, together with some nonheterocyclic compounds. The opium alkaloids contain representatives of the first four types. The curare alkaloids contain the last type.

Cactus Alkaloids.—This series, isolated from the Anhalonium species, contains a number of compounds, some of which are in the state just prior to formation of the isoquinoline nucleus. The formulas of a few of these are shown in Fig. 2.



Hordenine (Anhaline)

Mescaline

Anhalamine

Pellotine

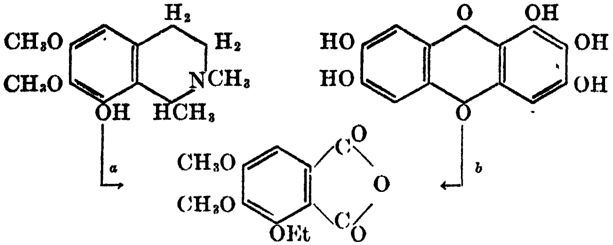
Anhalonidine

FIG. 2.—Some alkaloids of the cactus group.

The position of the hydroxy group in pellotine (and in anhalonidine also) is shown by a comparison of the oxidation product of the ethoxy derivative with that from the known rufigallic acid.[46]

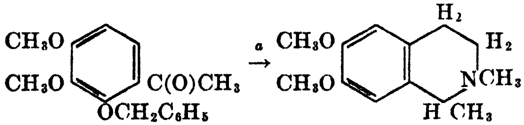
---

[46] SPÄTH and PASSL, *Ber.*, **65**, 1778 (1932); *cf.* SPÄTH, *Monatsh.*, **42**, 97 (1921); SPÄTH and RODER, *ibid.*, **43**, 93 (1922); SPÄTH, *ibid.*, **43**, 477 (1923).



[a] CH_3CHN_2, $KMnO_4$. [b] CH_2N_2 methylates the two hydroxy groups at C_2 and C_3, CH_3CHN_2 then ethylates the hydroxy group at C_1 which has a slower alklylation rate than the others because it is adjacent to the carbonyl group. $KMnO_4$ eliminates one ring.

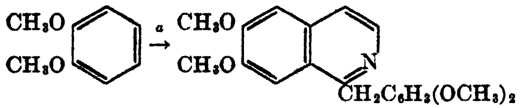
The synthesis of mescaline is, of course, a conventional preparation of a β-phenylethylamine; that of pellotine[47] is accomplished by the steps outlined below. The benzyl group is frequently used in these syntheses because later it can be preferentially removed by hydrolysis.



[a] $H_2NCH_2CH(OEt)_2$, 73 per cent H_2SO_4 (the benzyl group is removed), CH_3I, reduction.

The Opium Alkaloids.—The physiological activity of the opium (Greek word for "poppy head") alkaloids[48] has created a great interest in the chemistry of these compounds. Studies have progressed in two general directions: (*a*) to discover the structure of these compounds by degradative and preparative methods, and (*b*), to prepare, if possible, compounds related to them which would have their valuable physiological characteristics without their dangerous habit-forming properties.

The first and simplest of these alkaloids is illustrated by *papaverine*[49] (see Fig. 1). It is named from the plant *Papaver somniferum* L., where it is found in all parts except the root. It was discovered as a crystalline compound in the mother liquor obtained by extraction of morphine. Its synthesis follows the conventional steps already described for isoquinoline compounds. A β-(3,4-dimethoxyphenyl)-ethyl amine is prepared (see 3, Table I), the appropriate acyl derivative is formed with homoveratroyl chloride, and the ring is closed.



[a] $CH_3C(O)Cl$, HNO_2, Sn + HCl. Homoveratroyl chloride $(CH_3O)_2C_6H_3CH_2C(O)Cl$, reduction of carbonyl group to a secondary alcohol, P_2O_5 to close the ring and form the double bond. The

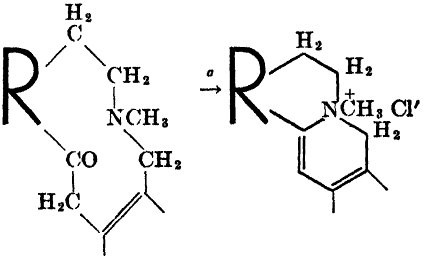
---

[47] SPÄTH and BOSCHAN, *Monatsh.*, **63**, 141 (1933).

[48] SMALL, Chemistry of the Opium Alkaloids, *U.S. Pub. Health Repts, Suppl.* 103 (1932).

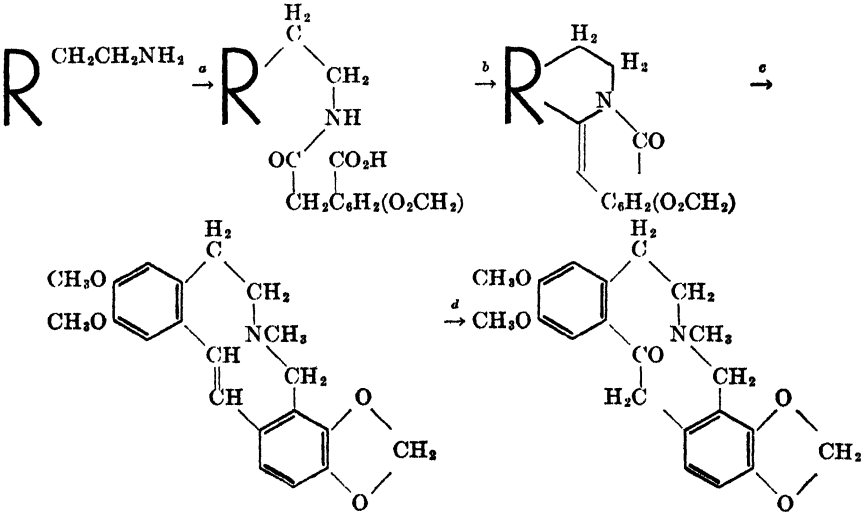
[49] PICTET and GANS, *Ber.*, **42**, 2943 (1909); *Compt. rend.*, **142**, 210 (1909).

The second class of alkaloids is represented in the opium group by *isocryptopine*, which is derived from cryptopine (from the Greek word meaning "cellar"), an alkaloid present only to the extent of 0.003 per cent and not discovered until the mother liquors, left after separation of other alkaloids, had been stored below ground for some time.[48] Cryptopine is readily converted to isocryptopine chloride by way of enolization and salt formation as shown by partial formulas below.



[a] $POCl_3$, $CH_3C(O)Cl$, or HCl.

The preparation of these two compounds (see Fig. 3) now appears relatively simple by a series of steps that furnishes many beautiful illustrations of well-known chemical processes in the isoquinoline series.



[a] 3,4-Methylenedioxyhomophthalic anhydride, $CH_2O_2C_6H_2(CO)_2O$.
[b] $POCl_3$.
[c] Reduction of the olefin bond prior to exhaustive methylation, CH_3I, AgCl, Hofmann degradation.
[d] Perbenzoic acid to form the N oxide, rearrangement of oxygen from nitrogen to carbon in CH_3CO_2H + HCl.

FIG. 3.—Steps for the synthesis of cryptopine.

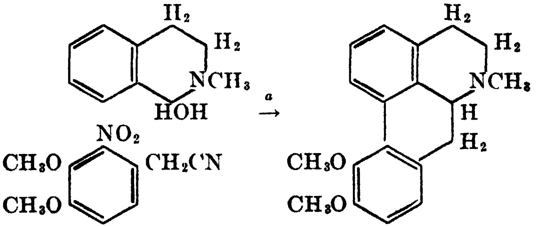
---

homoveratroyl chloride is prepared from vanillin by way of the following compounds: $(CH_3O)_2C_6H_3CHO$, $(CH_3O)_2C_6H_3CH(OH)CN$, $(HO)_2C_6H_3CH_2CO_2H$, $(CH_3O)_2C_6H_3CH_2CO_2H$, $(CH_3O)_2C_6H_3CH_2C(O)Cl$.

Synthesis[50] of the 10-membered ring compounds begins with homoveratroylamine, itself prepared from vanillin by one of the general methods used for the synthesis of β-phenylethyl amines. The first stage consists of the preparation of the berberine type compound and the second consists of ring opening and formation of the N-oxide which is convertible to cryptopine.

Apomorphine, a phenanthripyridine compound, results when morphine is treated with 35 per cent hydrochloric acid at 140 to 150°, with hot phosphoric acid, or with zinc chloride solution. It is also obtained from codeine. Its structure is suggested by (*a*) formation of a dibenzoyl derivative, indicative of two hydroxyl groups; (*b*) exhaustive methylation which yields a dimethoxyvinylphenanthrene, which in turn is oxidized to 3,4-dimethoxyphenanthrene-8-carboxylic acid; (*c*) vigorous benzoylation which yields a tribenzoyl derivative, which in turn is converted to a 9,10-phenanthraquinone by oxidation.

Synthesis[51] of the dimethyl ether, shown below, utilizes the reactivity of a methylene adjacent to a nitrile group for the first step.



[a] Condensation under the influence of sodium in alcohol, hydrolysis and decarboxylation by hot concentrated hydrochloric acid, reduction by tin and hydrochloric acid, and treatment with nitrous acid in sulfuric acid.

The remaining steps consist of hydrolysis of the nitrile group, elimination of carbon dioxide from the acid so produced, reduction of the nitro to an amino group, and closure to a phenathrene by a conventional process of diazotization (the Pschorr phenathrene ring closure).

Apomorphine hydrochloride is used[52] as an emetic.

The structure of *morphine* can be inferred only from its degradation products. The suggestion (Fig. 4) of Gulland and Robinson[53] is in agreement with the facts so far found.

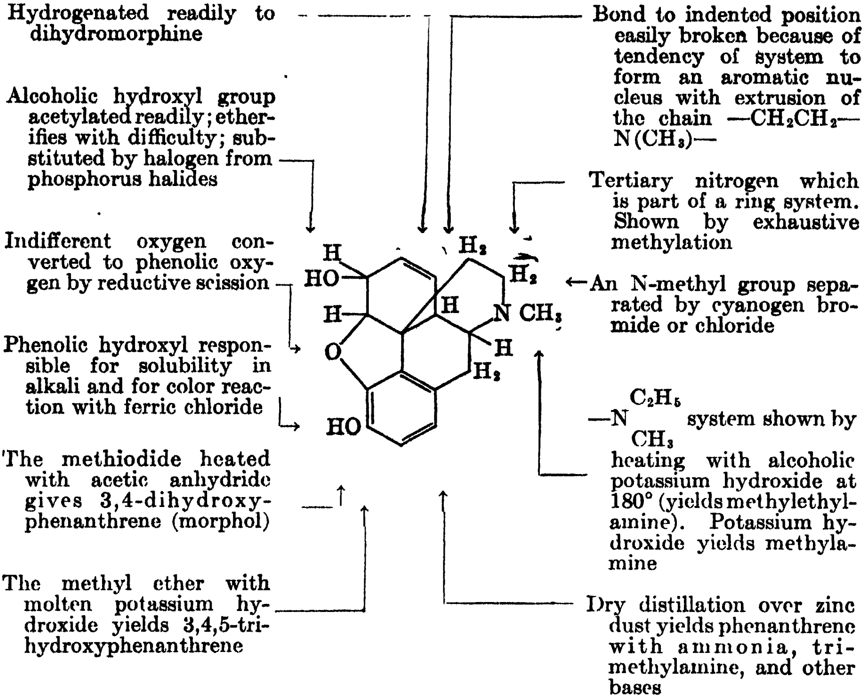
---

[50] Haworth and Perkin, *J. Chem. Soc.*, 1769 (1926); *cf.* Haworth, Perkin, and Pink, *ibid.*, **127**, 1709 (1925).

[51] Avenarius and Pschorr, *Ber.*, **62**, 321 (1929).

[52] Goodman and Gilman, "Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

[53] Gulland and Robinson, *J. Chem. Soc.*, **123**, 980 (1923); *Mem. Proc. Manchester Lit. & Phil. Soc.*, **69**, 79 (1925).



Hydrogenated readily to dihydromorphine

Alcoholic hydroxyl group acetylated readily; etherifies with difficulty; substituted by halogen from phosphorus halides

Indifferent oxygen converted to phenolic oxygen by reductive scission

Phenolic hydroxyl responsible for solubility in alkali and for color reaction with ferric chloride

The methiodide heated with acetic anhydride gives 3,4-dihydroxyphenanthrene (morphol)

The methyl ether with molten potassium hydroxide yields 3,4,5-trihydroxyphenanthrene

Bond to indented position easily broken because of tendency of system to form an aromatic nucleus with extrusion of the chain $—CH_2CH_2—N(CH_3)—$

Tertiary nitrogen which is part of a ring system. Shown by exhaustive methylation

←An N-methyl group separated by cyanogen bromide or chloride

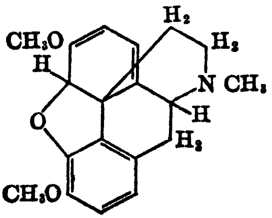
$—N\begin{smallmatrix}C_2H_5\\CH_3\end{smallmatrix}$ system shown by heating with alcoholic potassium hydroxide at 180° (yields methylethylamine). Potassium hydroxide yields methylamine

Dry distillation over zinc dust yields phenanthrene with ammonia, trimethylamine, and other bases

Fig. 4.—Probable structure of morphine and some facts that support it.

Codeine, named from the Greek word for "poppy seed," is the phenolic O-methyl ether of morphine. It is more stable to oxidizing agents than is morphine.

Thebaine is the dimethyl ether of morphine less two hydrogen atoms but with an extra double bond. The name is derived from the Egyptian city of Thebes where a certain type of opium was once produced.



Heroin, also known as diamorphine or acetomorphine, is the diacetyl derivative of morphine. It is prepared by the action of acetic anhydride or of acetyl chloride on morphine.

In addition to the physiological applications, opium can be used as an agent for detecting formaldehyde.[54] The phenolic group of the alkaloid combines with the aldehyde under the influence of strong sulfuric acid. A purple red to purple color is formed. In the presence of an oxidizing agent, the test is sensitive to 1 part in a million.

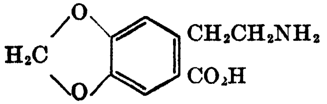
---

[54] Fulton, *Ind. Eng. Chem., Anal. Ed.,* 3, 200 (1931).

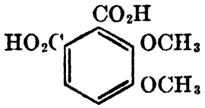
One of the major problems in chemistry is to find a derivative of, or substitute for, morphine that will have the good properties without the harmful characteristics of morphine.[55] In the course of such work, many derivatives of diphenylene oxide and of phenanthrene have been prepared and tested.

Berberine and Related Compounds.—This alkaloid is very widely distributed. It is only moderately toxic. Its chief use in medicine has been to impart a bitter taste (*e.g.*, barberry bark), although in recent years it has been applied to the treatment of Oriental sore.

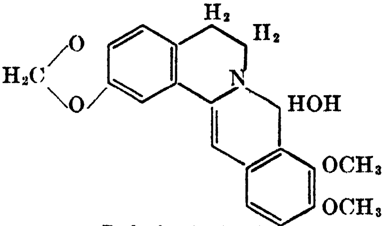
The structure of berberine ($C_{20}H_{19}O_5N$) is inferred[56] from the following essential facts: (*a*) Two methoxy groups are present. (*b*) Hydriodic acid demethylates it to berberoline, $C_{18}H_{13}O_4N$. (*c*) Warm alkaline permanganate oxidizes it to berberilic acid, $C_{20}H_{19}O_9N$, a dibasic acid, which in turn is hydrolyzed by hot sulfuric acid to *o*-(β-aminoethyl)-piperonylic acid (*A*) and hemipinic acid (*B*).



A

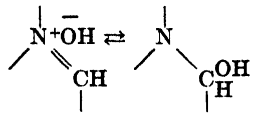


B

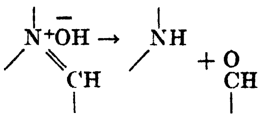


Berberine (carbinol form)

Berberine is believed to exist in an ammonium form (partial formula) and a carbinol form. The ammonium form exists in solution when the calculated quantity of barium hydroxide is added to an aqueous solution of the sulfate. It is responsible for ring scission[57] with caustic alkali by which an aldehyde, convertible to an oxime, is produced as shown by the partial formulas below.



Onium Carbinol



Alkali cleavage

Curare Alkaloids.—These compounds occur in the plant extracts[58] used by the Indians in the Orinoco and Amazon Valley region to poison arrows.[59] The material as prepared by the natives is known as tubocurare, pot curare, or calabash curare, depending on whether it is packed in bamboo tubes, earthenware pots, or gourds. There may be some difference also in the type of curare in each, since the method of preparation, as well as the plants, varies with the district. The drug is reported to be nontoxic when taken by mouth because it is absorbed by the intestinal mucous membrane and eliminated rapidly. When injected hypodermically, it rapidly paralyzes the motor nerve endings so that voluntary movement ceases, and causes death by respiratory failure. The alkaloid has been valuable as a muscular relaxant to reduce the dangers in shock therapy.

---

[55] VAN DE KAMP and MOSETTIG, *J. Am. Chem. Soc.*, **57**, 1107 (1935).

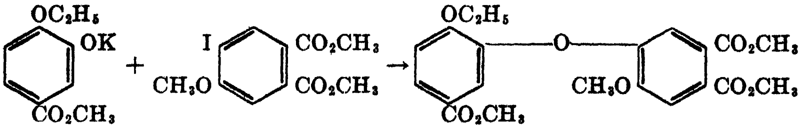
[56] PERKIN, *J. Chem. Soc.*, **55**, 63 (1889); **57**, 992 (1890); **97**, 305 (1910).

[57] TINKLER, *ibid.*, **99**, 1340 (1911).

[58] HENRY, "The Plant Alkaloids," 3rd ed., The Blakiston Company, Philadelphia, 1939.

[59] GILL, "White Water and Black Magic," Henry Holt and Company, Inc., New York, 1940; BENNET, *Am. Scientist*, **34**, 424 (1946).

King[60] has determined the structure of the methochloride of bebeerine, a diastereoisomer of tubocurarine chloride. The work furnishes a fine example of the now nearly routine steps that are employed in this work. Ultimate analysis and molecular weight show an empirical formula of $C_{36}H_{38}N_2O_6$. Presence of two phenolic and two methoxy groups is shown by conventional tests. Both nitrogen atoms are basic. The two phenolic groups are converted (sodium salt and ethyl iodide) to ethoxy groups in order to distinguish them from methoxy, the compound is converted to the methiodide salt and thence by silver chloride to the methochloride, and the salt is then subjected in sequence to a two-stage Hofmann degradation and permanganate oxidation to give a mixture of two acids, each with the composition $C_{18}H_{16}O_9$, each with one methoxy and one ethoxy group (see Fig. 5). By means of certain deductions made from the behavior of Millon's reagent with substituted phenols, it appears reasonable to believe that the ethoxy group in acid B represents the position of one of the phenolic groups in the original alkaloid. This acid is obtained by condensation of the potassium salt of methyl 3-hydroxy-4-ethoxybenzoate with methyl 5-iodo-4-methoxyphthalate in the presence of copper. The desired compound is isolated from the mixture of products obtained.

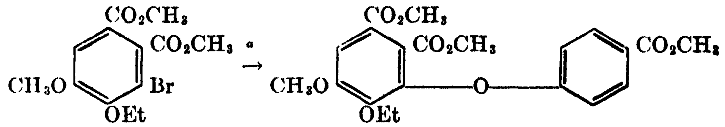


The phenolester is obtained by hydrolysis (HBr 1.3) of O-ethylvanillic acid followed by esterification. The phthalate is obtained by methylation of o-4-xylanol, oxidation of the methyl ether by permanganate to 4-methoxyphthalic acid, and a conventional sequence of nitration, reduction, diazotization, and iodination.

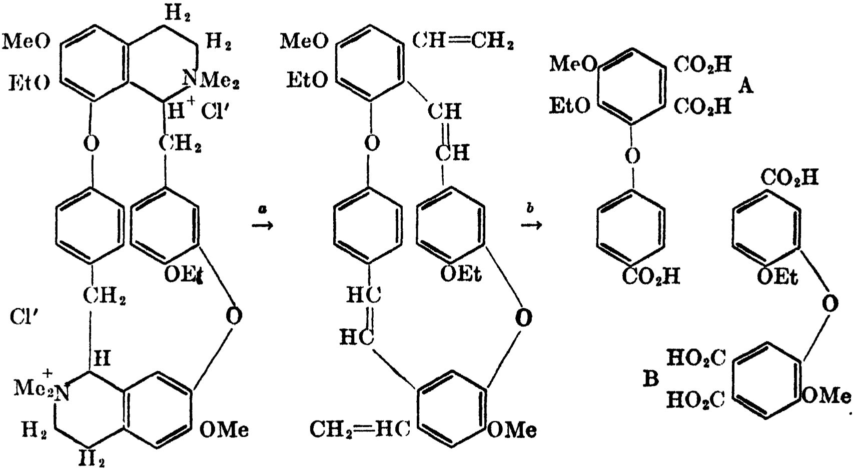
The other acid (A) is prepared readily by conversion (sodium hydroxide and copper) of the above iodo compound to a hydroxy derivative, which by bromination changes to 3-bromo-4-hydroxy-5-methoxy phthalic acid. The dimethyl ester of this acid is ethylated by diazoethane, and this product is in turn treated as in the equation below in order to give the desired compound. A suggested assembly of the parts to give the curare alkaloid has already been given in Fig. 1.

---

[60] King, *Ann. Repts*, **30**, 242 (1934); *J. Chem. Soc.*, 1472 (1937); 1157 (1939); 737 (1940).



[a] Reaction with p-$KOC_2H_4CO_2CH_3$.



[a] Hofmann degradation. [b] $KMnO_4$ oxidation.

FIG. 5.—Degradation of the diethoxy derivative of the methochloride of bebeerine.

Problems

1. What is the product of the following reactions? (*a*) Phenylethylbenzamide heated in 10 parts of toluene with 2 parts of phosphorus pentoxide.[3] (*b*) Veratraldehyde and acetone treated with 10 per cent sodium hydroxide to give a compound of the composition $C_{21}H_{22}O_5$, which with hydrogen over PtO_2 gives $C_{21}H_{26}O_5$, which in turn with hydroxylamine, and then with phosphorus oxychloride in toluene for 2 hr. at 120 to 130° (oil bath temperature), yields $C_{21}H_{25}O_4N$.[16] (*c*) *o*-Veratraldehyde, 2,3-$(CH_3O)_2C_6H_3CHO$, heated with aminoacetal, the product dissolved in sulfuric acid, and the solution saturated with hydrogen chloride.[61] (*d*) *o*-Chlorobenzaldehyde heated in an oil bath with aminoacetal (how prepared?) until the liberated water is removed, and the product of the reaction then heated with a mixture of sulfuric acid and phosphorus pentoxide at 160 to 164°.[62] (*e*) Homoveratroylhomoveratrylamine allowed to react with phosphorus oxychloride, then aerially oxidized and treated with alcoholic potash to give $C_{20}H_{19}NO_5$.[63] (*f*) *p*-Bromotoluene, converted to the Grignard reagent, and then treated with ethylene chlorohydrin; the product of this

[61] PERKIN, JR., and ROBINSON, *J. Chem. Soc.*, **105**, 2376 (1914).

[62] KEILIN and CASS, *J. Am. Chem. Soc.*, **64**, 2442 (1942).

[63] BUCK, HAWORTH, and PERKIN, JR., *J. Chem. Soc.*, **125**, 2176 (1924).

reaction treated with strong hydrobromic acid and subsequently with potassium phthalimide; the phthalimide treated with hydrochloric acid; the hydrolysis product treated with ethyl bromoacetate and then with concentrated hydrochloric acid to $C_{11}H_{15}NO_2$, which is treated in sequence with benzenesulfonyl chloride, phosphorus pentachloride, aluminum chloride, and finally with hydrochloric acid at 130°.[7]

2. Name the product that is formed in each step of the following sequence of reactions which begins with veratraldehyde, 3,4-$(CH_3O)_2C_6H_3CHO$, and employs each of the reagents named in turn on the product of the preceding step: (*a*) Hippuric acid, sodium acetate, and acetic anhydride. (*b*) Dry calcined soda in methanol to yield $C_{19}H_{19}O_5N$. (*c*) Hydrogen over platinum oxide at a pressure of 3 atm. (*d*) Phosphorus pentoxide in boiling xylene. (*e*) Dilute acid permanganate.[64]

3. The following reactions of isoquinoline are, in general, very similar to those of pyridine, piperidine, or quinoline. What is the product of, the reaction of, the following? (*a*) Isoquinoline with zinc and hydrochloric acid or sodium and absolute alcohol.[65] (*b*) Isoquinoline and fuming sulfuric acid.[66] (*c*) Tetrahydroisoquinoline and hydrogen peroxide.[67] (*d*) N-Benzoyltetrahydroisoquinoline and alkaline potassium permanganate.[68] (*e*) Isoquinoline and nitric-sulfuric acid mixture.[69] (*f*) Isoquinoline sulfate treated with fuming (50 per cent SO_3) sulfuric acid at 20 to 25° for 48 hr. and the product subjected in sequence to caustic alkali, diazotized aniline, sodium hydrosulfite, and finally a 20 per cent solution of ferric chloride.[70] (*g*) Isoquinoline with ethyl acetylenedicarboxylate.[71] (*h*) Isoquinoline with butyllithium and the product of this reaction either treated with water or heated in a nitrobenzene solution.[72] (*i*) Acid hydrolysis of the product of the reaction of isoquinoline, benzoyl chloride, and potassium cyanide.[73] (*j*) Isoquinoline fused with potassium hydroxide at 220°.

4. What chemical method could be used to differentiate isoquinoline from quinoline?[74]

5. Complete the steps necessary for the preparation of 4-methylisoquinoline from *o*-cyanobenzylcyanide.[23]

6. What is the probable product obtained from the reactions of apomorphine with cyanogen bromide?[75]

7. What is the product of the following sequence of reactions? A mixture of phenylnitromethane and piperonal is heated with a few drops of ethyl- or amyl-amine, and the product of this reaction is dissolved in pyridine and reduced with hydrogen in the presence of palladium-carbon until 2 molecules of hydrogen are absorbed to give a compound that has the composition $C_{15}H_{13}O_3N$. This material in turn is refluxed with 3 per cent sodium amalgam in alcohol solution to give a compound

---

[64] HARWOOD and JOHNSON, *J. Am. Chem. Soc.*, **56**, 468 (1934).

[65] HOOGEWERFF and VAN DORP, *Rec. trav. chim.*, **5**, 310 (1886); BAMBERGER and DIECKMANN, *Ber.*, **26**, 1205 (1893); LADENBERG, *Ber.*, **27**, 854 (1895).

[66] CLAUS and SEELERMANN, *J. prakt. Chem.* [2], **52**, 1 (1895).

[67] MAASS and WOLFFENSTEIN, *Ber.*, **30**, 2189 (1897); **31**, 2689 (1898).

[68] BAMBERGER and DIECKMANN, *Ber.*, **26**, 1205 (1893).

[69] FORTNER, *Monatsh.*, **14**, 146 (1893); DECKER, *J. prakt. Chem.* [2], **47**, 40 (1893); CLAUS and HOFMANN, *J. prakt. Chem.* [2], **47**, 252 (1893).

[70] FIESER and MARTIN, *J. Am. Chem. Soc.*, **57**, 1840 (1935).

[71] DIELS, ALDER, *et al.*, *Ann.*, **498**, 16 (1932).

[72] ZIEGLER and ZEISER, *ibid.*, **485**, 174 (1931).

[73] REISSERT, *Ber.*, **38**, 3426 (1905).

[74] HOOGERWERFF and VAN DORP, *Rec. trav. chim.*, **4**, 289 (1885).

[75] V. BRAUN and AUST, *Ber.*, **50**, 43 (1917).

(analysis of the acetic acid salt is $C_{17}H_{19}O_4N$) that is at first gently warmed in aqueous solution with 35 per cent formaldehyde solution and then heated on the water bath for 1 hr. to complete the reaction. When again warmed with 10 per cent hydrochloric acid, a crystalline compound is obtained which, when freed from hydrochloric acid, has the composition $C_{16}H_{15}O_2N$. Permanganate oxidation then gives a compound of the composition $C_{16}H_{11}O_2N$. How would either of the last two compounds be degraded in order to prove its constitution?[76]

8. The following facts, combined with a good knowledge of the chemistry of alkaloids, enabled Perkin, Jr., to arrive at the correct structure for a certain alkaloid.[77] Arrange the facts in logical order and decide what structure best represents the facts. and account for all products.

The alkaloid has the composition $C_{21}H_{23}NO_5$. It is optically inactive and cannot be resolved by crystallization of the tartrate. Dilute nitric acid converts it to $C_{21}H_{22}N_2O_7$. Permanganate converts the hydrochloride salt of the alkaloid to a compound shown to be identical with *m*-hemipinic acid, which is 4,5-dimethoxyphthalic acid. The deep violet solution of the alkaloid in sulfuric acid (*a*) gives a red coloration with phloroglucinol, and a red precipitate when heated with that reagent on a water bath; (*b*) turns colorless at first and then becomes green on addition of a 5 per cent solution of gallic acid in alcohol. The alkaloid combines readily with methyl sulfate to give the methosulfate $C_{21}H_{23}O_5N \cdot Me_2SO_4$ and this compound is reduced in boiling acid solution with sodium amalgam to give a product of the composition $C_{22}H_{29}O_5N$. The reaction of acetyl chloride with this last product yields, by elimination of water, an anhydro base of the composition $C_{22}H_{27}O_4N$. This base when oxidized by dry potassium permanganate in acetone solution yields five products, one of which is the above-mentioned hemipinic acid and another is a sirupy base of the composition $C_{13}H_{19}O_3N$ which has two methoxy groups and forms a methiodide, $C_{13}H_{19}O_3N \cdot CH_3I$, and an oxime. This last methiodide is converted by boiling potassium hydroxide to trimethylamine and another aldehyde whose semicarbazone has the composition $C_{12}H_{15}O_3N_3$. A third product of this permanganate oxidation is a monobasic acid of the composition $C_{13}H_{17}O_5N$ which, heated in the dry state, gives a compound shown to be identical with 6,7-dimethoxy-2-methyltetrahydroisoquinoline.

The fourth and fifth products of this oxidation were, respectively, an aldehyde $C_9H_8O_3$ and an acid $C_9H_8O_4$. The aldehyde had no methoxy group, but after a sequence of treatment with phosphorus pentachloride, formic acid, and boiling water (which yielded, respectively, $C_9H_6O_3Cl_2$, $C_9H_6O_4$, and $C_8H_8O_3$) gave a material $C_8H_8O_3$ that was methylated by methyl sulfate in the presence of sodium ethoxide to give a product that had the composition $(CH_3O)_2C_6H_2(CH_3)CHO$ and that was not identical with 4,5-dimethoxy-*o*-tolualdehyde.

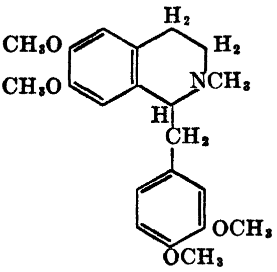
The position of the methyl group was determined by oxidation of this aldehyde, $C_9H_8O_3$, to the corresponding acid $C_9H_8O_4$, which is identical with the acid mentioned above as the fourth product. Attempts to oxidize the methyl group in this acid resulted in complete degradation. The acid was therefore subjected to the same sequence of treatments (PCl_5, HCOOH, H_2O) as were applied to the aldehyde, and the dihydroxy acid was then methylated to a dimethoxy compound $(CH_3O)_2C_6H_2(CH_3)COOH$, which was sufficiently stable when oxidized by permanganate to give a compound already known as hemipinic acid, or 3,4-dimethoxyphthalic acid. Furthermore, the dihydroxy acid is decomposed by heating with water at 170 to 180° to 2,3-dihydroxytoluene, otherwise known as *iso* homocatechol.

When the original alkaloid was reduced to a tetrahydro compound, and the anhydro base converted to the methosulfate, and this salt was in turn digested with methylalcoholic potassium hydroxide, trimethylamine was eliminated and a compound having the composition $C_{20}H_{20}O_4$ was obtained. This compound in turn was oxidized by permanganate to give five products, *viz.*, 5,6-methylenedioxy-*o*-tolualdehyde, 5,6-methylenedioxy-*o*-toluic acid, 4,5-dimethoxy-2-vinylbenzaldehyde, *m*-opianic acid (4,5-dimethoxy-2-aldehydobenzoic acid), and *m*-hemipinic acid.

---

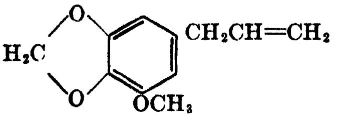
[76] Reichert and Hoffmann, *Arch. Pharm.*, **274**, 153 (1936).

[77] Perkin, *ibid.*, **109**, 815 (1916).

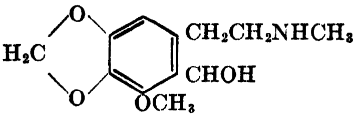


9. Laudosine is of special interest because it was the first opium alkaloid that was totally synthesized. Its structure is indicated on the left. Suggest a sequence of reactions for its synthesis[78] from nonheterocyclic materials.

10. Cotarnine is an oxidation (manganese dioxide and sulfuric acid) product of the naturally occurring alkaloid narcotine. Suggest a method for its synthesis that will employ myristicin as the starting reagent and will progress to cotarnine through a heterocyclic compound.[79]



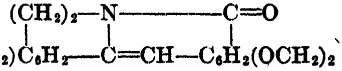
Myristicin



Cotarnine

11. What is the probable structure of an alkaloid that has the empirical formula $C_{20}H_{21}NO_4$, and that has the following properties? (*a*) Reaction with hydriodic acid yields methyl iodide. (*b*) Fuming hydrochloric acid at 130° yields methyl chloride and homopyrocatechol. (*c*) Neutral potassium permanganate yields veratric acid (3,4-dimethoxybenzoic acid), metahemipinic acid (4,5-dimethoxyphthalic acid), and 1,2,3-pyridinetricarboxylic acid. (*d*) Fusion with caustic potash yields dimethylhomopyrocatechol, $C_9H_{12}O_2N$, a compound that is oxidizable to veratric acid.[80]

12. Oxyberberine, $C_{20}H_{17}O_5N$, is obtained from berberine by addition of barium hydroxide to the sulfate solution, conversion to the aldehyde form of berberine by addition of excess of sodium hydroxide, and then formation of the oxime, which, with concentrated sodium hydroxide, yields oxyberberine. The result of these changes is believed to have the structure



$$\begin{array}{ccccc} (CH_2)_2 & - & N & \text{---------} & C{=}O \\ | & & | & & | \\ (CH_2O_2)C_6H_2 & - & C{=}CH & - & C_6H_2(OCH_3)_2 \end{array}$$

Devise a synthesis for this compound.[81]

---

[78] Pictet and Finkelstein, *Ber.*, **42**, 1979 (1909).

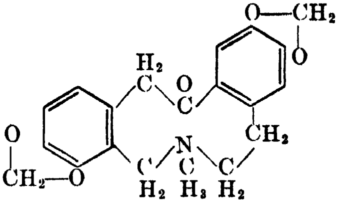
[79] Salway, *J. Chem. Soc.*, **97**, 1208 (1910).

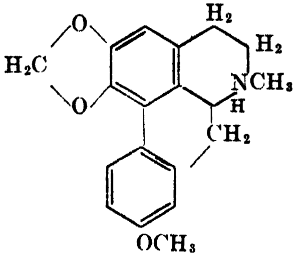
[80] Goldschmidt, *Monatsh.*, **9**, 762 (1882); Rossin, *ibid.*, **12**, 486 (1891).

[81] Haworth, Koepfli, and Perkin, Jr., *J. Chem. Soc.*, 548 (1927); *cf.* Späth and Quietensky, *Ber.*, **58**, 2267 (1925); Perkin, Rây, and Robinson, *J. Chem. Soc.*, **127**, 740 (1925).

13. Suggest a method for the synthesis of 7-hydroxyisoquinoline, the starting point in the preparation of the piperidine part in the synthesis of quinine.[82]

14. Suggests a method of synthesis for protopine[83] and for *l*-ON-dimethylanolobine[84] which have the formulas shown





---

[82] Woodward and Doering, *J. Am. Chem. Soc.*, **67**, 860 (1945).

[83] Perkin, *J. Chem. Soc.*, **109**, 1023 (1916); Haworth and Perkin, *ibid.*, 1769 (1926).

[84] Marion, *J. Am. Chem. Soc.*, **66**, 1125 (1944).

CHAPTER XII

ACRIDINES AND OTHER CONDENSED COMPOUNDS

In addition to the quinoline and isoquinoline compounds, discussed in the previous chapters, there exist a number of other condensed systems in which the pyridine ring is fused to two or more benzene rings or with other heterocyclic rings. Some of these, such as the acridines, have practical value as pharmaceuticals or dyes; others, such as *o*-phenanthroline, are useful in analytical work; and still others, such as the harmala and valuable ergot alkaloids, occur in nature. The chemistry of the compounds is much like that of the simpler ones, though complicated by the larger size of the molecule.

Naming and Numbering.—The numbering of mono- and bi-cyclic heterocyclic compounds offers no special problem, but that of tri-cyclic and larger systems is frequently confusing. The older methods were usually based on the relationship to compounds of low molecular weight such as quinoline, isoquinoline, indole, carbazole, and the like. As more complicated compounds were prepared, the numbering became correspondingly involved. Two systems are now generally employed: that used in Beilstein, which bases the numbering and naming on the origin of the compound, and that employed in "The Ring Index," which numbers according to a given set of rules irrespective of the source or components of the system. This last plan, as published in "The Ring Index"[1] and used in *Chemical Abstracts*, has the approval of the Committee on Organic Nomenclature of the International Union of Chemistry (1938) and is applicable to all condensed systems except acridine, anthracene, carbazole, cyclopenta[α]phenanthrene (the parent of the sterols), phenanthrene, the purines and xanthene, the numbering of which was originally made on an empirical basis but has long been accepted as standard.

The best of numbering systems will sometimes fail to be satisfactory, and the arrangement that is correct for numbering may often fail to show significant parts of the molecule in proper perspective. This failure will be seen to be especially true in the case of the formula for the ergot alkaloids and for cytisine. Nevertheless, some general system should be followed. The one given in "The Ring Index" has many excellent points, is comparatively easy to understand, and is available in book form for consultation. With respect to numbering, this text conforms to that system, except for the compounds noted above; with regard to naming, it prefers to use the simple names wherever the meaning is clear; and with regard to writing the formula right-side up or upside-down or otherwise, it makes no discrimination in the case of smaller molecules, where the numbering is easy to follow, but generally conforms to the right-side up scheme in the case of the more complicated compounds, such as are described in this chapter. In some cases, *e.g.* quinoline red, the formula is written in two different positions in order to reveal aspects of structure that explain the chemical behavior.

---

[1] Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, 1940.

Acridine is one of the systems that is an exception to the general rule.[2] Its numbering, shown in Fig. 1, follows that used for anthracene. The nitrogen atom is regarded as in the 10-position, so that substituents in the meso position will have as low a number as possible.

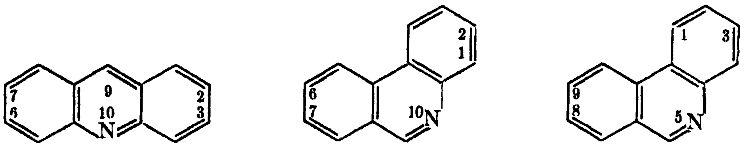
Phenanthridine might be numbered as is the phenanthrene molecule, a logical enough practice if acridine is to be patterned after anthracene. The numbering in Beilstein follows this rule. If phenanthridine is numbered according to "The Ring Index," the nitrogen atom is 5, as shown in Fig. 1.

In "The Ring Index," all compounds, for purposes of numbering, are written in such a way as to make the longest horizontal row of rings possible, with the maximum number of rings in the upper right quadrant formed by bisecting the horizontal line. If two or more alternative arrangements satisfy these requirements, the one that gives the second largest number of rings in the lower left quadrant and the lowest number to the hetero atom is preferred. Five-membered rings are written with the apex up wherever possible. The numbering then begins at the first free angle of the ring, which is the farthest right in the top row, and progresses clockwise around the molecule. No numbers are assigned to the indented position between two rings unless the atom happens to be nitrogen, since, usually, there are no substituents at these points. According to such a plan, the nitrogen atom of phenanthridine is numbered 5.

---

[2] If there were no exceptions to the numbering plan of "The Ring Index," the meso positions in anthracene would be 5,10-, instead of 9,10-. Anthracene was, of course, numbered as it now is in order to emphasize that the reactions in the 9,10-positions, between the two rings, were distinctly different from those at other positions. If the same logic was applied to all other ring systems, the confusion would be unending. Although custom has decreed that the meso positions of anthracene are to be labeled 9,10-, it would be equally easy to remember these positions if the numbering had been 5,10.

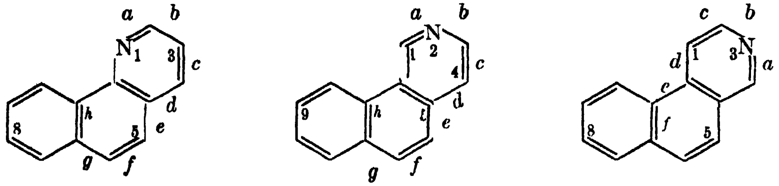
In cases where a trivial name, such as phenanthridine or phenanthroline, is not available, the compound is named as a fusion of two known systems. Benzoquinoline and pyridoquinoline are examples. The same principle of numbering is then followed, but the position of fusion is given by numbers and letters in brackets between the names of the



Acridine

Phenanthridine
(Beilstein)

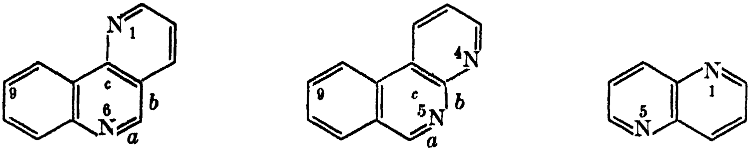
Phenanthridine
("The Ring Index")



Benzo[*h*] quinoline
7,8-Benzoquinoline
Naphtho-1′,2′:2,3-pyridine
α-Naphthoquinoline

Benzo[*h*]isoquinoline
7,8-Benzoisoquinoline
3,4-(Naphtha-1′,2′)-pyridine
Naphthisoquinoline

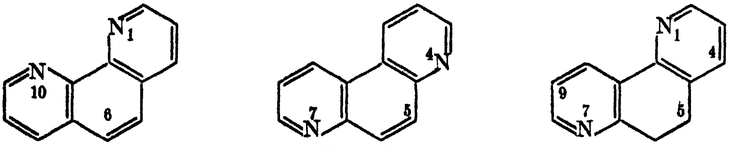
Benzo[*f*]isoquinoline
5,6-Benzoisoquinoline



Pyrido[3,2-*c*]quinoline
7,8-Benzo-1,6-naphthyridine
Pyridino-3′,2′:3,4-quinoline

Pyrido[2,3-*c*]isoquinoline
3,4-Benzo-1,8-naphthyridine
Pyridino-2′,3′:3,4-isoquinoline
Isoquino-β-pyridine

1,5-Naphthyridine
Pyrido[3,2,-*b*]-pyridine
1,5-pyridopyridine



1,10-Phenanthroline
o-Phenanthroline
1,8-Phenanthroline

4,7-Phenanthroline
p-Phenanthroline
1,8-Phenanthroline

1,7-Phenanthroline
m-Phenanthroline
1,5-Phenanthroline

FIG. 1.—Numbering and naming of acridine and related compounds. Key numbers only are shown.

two systems involved. The numbers in brackets have no relation to the numbering in the fused system but refer to the numbering in the first component of the fusion; the letters in the bracket refer to the side of the second component. For example, pyrido[3,2-*c*]quinoline means that a 3,2-position of a pyridine ring is fused with a *c* side of a quinoline system. The letters *a*, *b*, *c*, etc., for the side of the system are used in place of 1′,2′-, or 2′,3′-, or 3′,4′-, respectively, in order to avoid the use of extra sets of numbers. In the case of benzo[*h*-]quinoline, the numbers can obviously be omitted.

Several examples of the numbering and naming systems are given in Fig. 1. The first name under each compound is the one preferred by "The Ring Index." Other names are given below the preferred name. Some of these other names have considerable value. For instance, *o*-, *m*-, and *p*-phenanthrolines signify that the nitrogen atoms are located as in *o*-, *m*-, and *p*-phenylene diamine, respectively.

The confusion that can exist in numbering and naming is apparent from these comparatively simple cases, for most of which several alternatives are possible.

One of the great advantages of "The Ring Index" system is that all compounds, which have the same skeleton framework, have, in general, the same numbering system, irrespective of the atoms that comprise the frame or the position of the hetero atoms in the ring.

THE ACRIDINES

Preparation.—In general, acridine compounds are prepared by joining two aromatic rings by appropriately placed carbon and nitrogen atoms. The wide variety of substances employed in synthesis illustrates the great tendency for the system to form. Figure 2 shows some of the methods for making acridines, acridanes, and acridones. Where the product is an acridane, the final step to an acridine is made by a mild oxidizing agent such as ferric chloride, potassium ferricyanide, or dilute nitric acid; where it is an acridone, the conversion to an acridine, if desired, is effected by reduction, by distillation with zinc dust, or by treatment with phosphorus pentachloride and reduction.

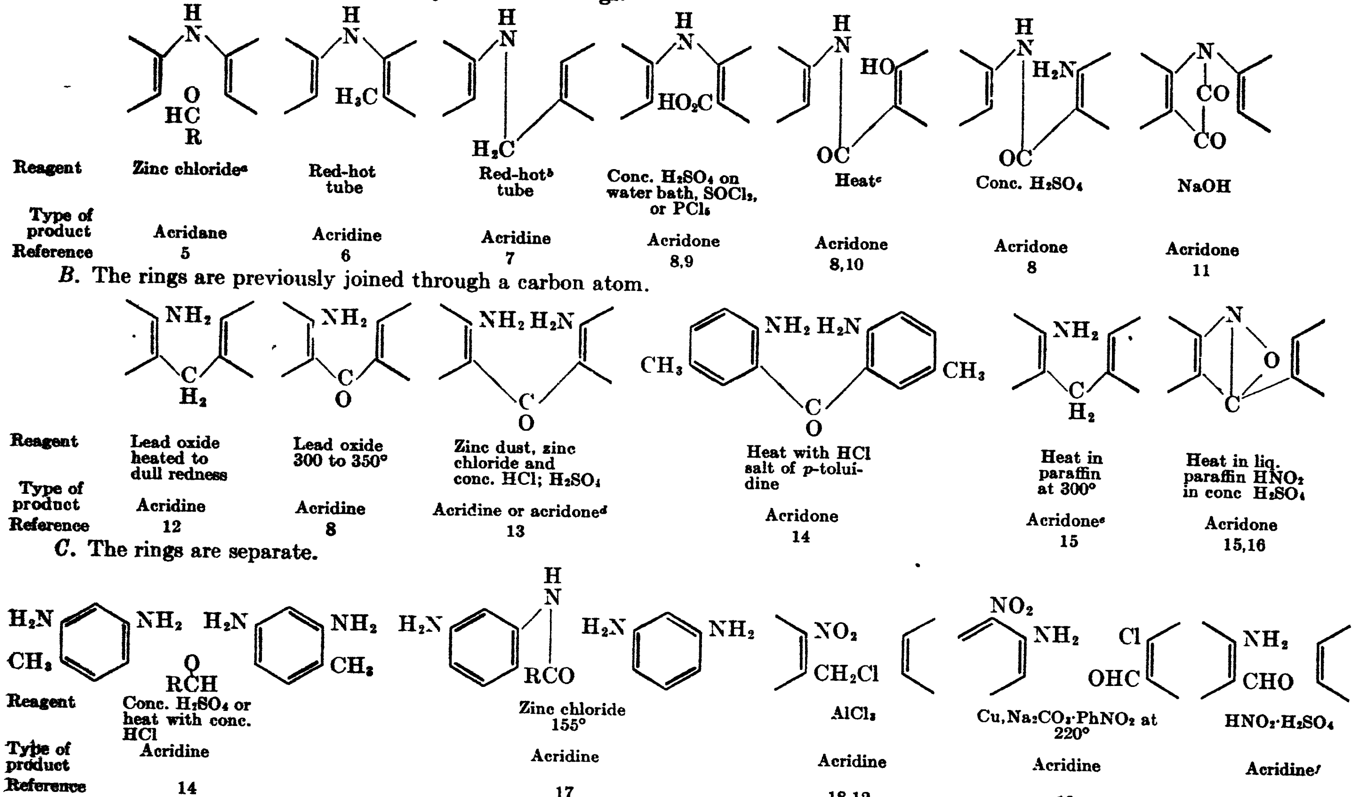
Of these processes, the ones that employ diphenyl amines and an aldehyde or other suitable carbonyl-containing group, or that use the closely related N-aryl-substituted anthranilic acid, or that have *m*-phenylene diamine as one component are the most common. All processes probably proceed through the formation of an intermediate diphenylamine, diphenylmethane, or diphenyl ketone.

General Properties.—The general properties of the acridines are those predicted from the chemistry of pyridine and quinoline coupled with some anthracene-like behavior. From the quinoline side, one expects and finds perhalide formation with bromine, nitration[3] in the benz rather than the pyridine ring (although the position taken by the nitro group is para to the nitrogen rather than adjacent to the pyridine ring), addition of alkyl- or aryl-lithium compounds across the 9,10-positions,[4] and the

---

[3] Jensen and Friedrick, *J. Am. Chem. Soc.*, **49**, 1049 (1927).

[4] Bergmann, Blum-Bergmann, and von Christiani, *Ann.*, **483**, 80 (1930); Ziegler and Zeiser, *Ann.*, **485**, 174 (1931).



A. A nitrogen atom is in the unit that joins the two rings.

Reagent	Zinc chloride[a]	Red-hot tube	Red-hot[b] tube	Conc. H_2SO_4 on water bath, $SOCl_2$, or PCl_5	Heat[c]	Conc. H_2SO_4	NaOH
Type of product	Acridane	Acridine	Acridine	Acridone	Acridone	Acridone	Acridone
Reference	5	6	7	8,9	8,10	8	11

B. The rings are previously joined through a carbon atom.

Reagent	Lead oxide heated to dull redness	Lead oxide 300 to 350°	Zinc dust, zinc chloride and conc. HCl; H_2SO_4	Heat with HCl salt of *p*-toluidine	Heat in paraffin at 300°	Heat in liq. paraffin HNO_2 in conc H_2SO_4
Type of product	Acridine	Acridine	Acridine or acridone[d]	Acridone	Acridone[e]	Acridone
Reference	12	8	13	14	15	15,16

C. The rings are separate.

Reagent	Conc. H_2SO_4 or heat with conc. HCl	Zinc chloride 155°	$AlCl_3$	Cu,Na_2CO_3·$PhNO_2$ at 220°	HNO_2·H_2SO_4
Type of product	Acridine	Acridine	Acridine	Acridine	Acridine[f]
Reference	14	17	18,12	19	22,23

FIG. 2.—Some combinations favorable for formation of acridine systems. Partial formulas are used as far as possible.

For footnotes a to f see opposite page.

customary activity of substituents in the 9-position, corresponding to the gamma-position in pyridine. An amino group in the 9-position suffers hydrolysis more readily than in other positions and forms no diazonium salt under normal conditions, although it will under highly acid ones.[24] A methyl group in the 9-position undergoes condensation readily with aldehydes and with *p*-nitrosodimethylaniline[25] (the anil is hydrolyzable to the aldehyde), and its products with formaldehyde,[26] chloral,[27] and *o*-nitrobenzaldehyde[28] are hydroxy compounds rather than the olefins. Methyl or alkyl acridinium salts form unstable -inium hydroxides and cyanides, the hydroxide or cyanide radical of which migrates from the 10- to 9-position, at which point conversion of the 9-hydroxy-9,10-dihydro product to an acridone, analogous to the pyridones, takes place with mild oxidizing agents such as potassium ferricyanide.[29] The size of the molecules and the comparative slowness of this change in the methyl acridinium compounds makes measurement

[24] Albert and Ritchie, *J. Chem. Soc.*, 458 (1943).

[25] Kaufmann and Valette, *Ber.*, **45**, 1736 (1912).

[26] Homberger and Jensen, *J. Am. Chem. Soc.*, **48**, 800 (1926).

[27] Bernthsen and Muhlert, *Ber.*, **20**, 1541 (1887).

[28] Sharp, Sutherland, and Wilson, *J. Chem. Soc.*, 654 (1938).

[29] Hantzsch and Kalb, *Ber.*, **32**, 3109 (1899); Tinkler, *J. Chem. Soc.*, **89**, 857 (1906); Aston, *J. Am. Chem. Soc.*, **53**, 1448 (1931).

---

[a] Among other reagents that may be used in place of the aldehyde, are chloroform and zinc oxide at 200 to 210°,[20] chloroform and aluminum chloride at 300°,[5] formic acid and zinc chloride at 270°,[5] crystalline oxalic acid and zinc chloride at 260°,[5] or oxallyl chloride.[11] Benzonitrile at 230 to 250° may also be used, in which case the product is 9-phenylacridine.[21]

[b] Phenanthridine is formed also. Benzaniline does not form acridine or phenanthridine. The acridine, therefore, does not come from an intermediate benzalaniline but probably by way of a rearrangement to *o*-aminodiphenylmethane.

[c] This condensation probably proceeds through the intermediate N-phenylanthranilic acid. Otherwise phenanthridone should result.[10]

[d] Zinc dust forms the acridine, zinc chloride, or sulfuric acid the acridone.

[e] 2-Aminobenzophenone is formed also.

[f] The intermediate product in this case is an anthranil (see p. 425) which need not be isolated.

[5] Bernthsen, *Ann.*, **224**, 1 (1884).

[6] Graebe, *Ber.*, **17**, 1370 (1884).

[7] Meyer and Hofmann, *Monatsh.*, **37**, 698 (1916).

[8] Graebe and Lagodzinski, *Ann.*, **276**, 35 (1893); *Ber.*, **25**, 1733 (1892).

[9] Schroeter and Eisleb, *Ann.*, **367**, 144 (1909).

[10] Pictet and Hubert, *Ber.*, **29**, 1189 (1896).

[11] Stollé *et al.*, *J. prakt. Chem.*, **128**, 1 (1930).

[12] Fischer and Schutte, *Ber.*, **26**, 3085 (1893).

[13] Staedel, *ibid.*, **27**, 3362 (1894); **26**, 3364 (1893).

[14] Ullmann, *ibid.*, **36**, 1017 (1903).

[15] Kliegl, *ibid.*, **42**, 591 (1909).

[16] Bamberger, *ibid.*, **42**, 1707 (1909).

[17] Albert, *J. Chem. Soc.*, 121 (1941).

[18] Koenig and Nef, *Ber.*, **19**, 2427 (1886).

[19] Mayer and Stein, *ibid.*, **50**, 1306 (1917).

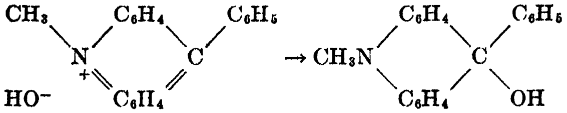
[20] Fischer and Korner, *ibid.*, **17**, 101 (1884).

[21] Bernthsen, *Ann.*, **192**, 19 (1878).

[22] Kliegl, *Ber.*, **41**, 1845 (1908).

[23] Lehmstedt, *ibid.*, **65**, 834 (1932).

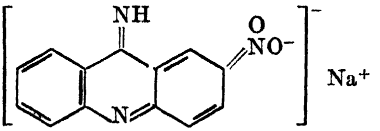
of the rate of change possible.[29] For example, the conductance of 9-phenylmethylacridinium hydroxide is high

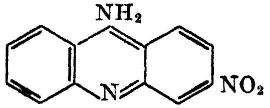


(μ = 117.5 at 0°) when first formed, is proportionately lower at 10 and 60 min. (μ = 57.4 and 14.1, respectively), and is approximately zero in 15 hr. 3-Amino-10-methylacridinium hydroxide is about 90 per cent ionized at M/276 and 0° and, therefore, is almost as strong as sodium hydroxide. In contrast to the rapid isomeric change of other bases, this base and 3,6-diamino-10-methyl-acridinium hydroxide resist boiling for a few minutes.[30]

From the anthracene-like structure stems the resistance of acridine-9-carboxylic acid[31] to esterification by alcohol and mineral acid catalyst and the need for preparing the ester from the acid chloride and alcohol. Unlike anthracene, however, acridine[32] forms no adduct with maleic anhydride.

Resonance can exist between substituents in the different rings. For example, 2-nitro- but not 3-nitro-9-aminoacridine gives a purple nitronate with alcoholic alkali.[24] Rearrangement of bonds is possible in the former, but not in the latter.





Compounds.—*Acridine* was discovered[33] in 1870 in a crude anthracene fraction from coal tar by extraction with dilute sulfuric acid. It melts at 107°, boils at 345 to 346°, and sublimes readily.[34] It is triboluminescent.[35] It crystallizes from hot water and dissolves readily in alcohol or ether. Dilute solutions have a blue fluorescence. It has a characteristic odor, causes sneezing and coughing, and irritates the skin; hence its name. As a base ($K_B = 3 \times 10^{-10}$), it is a little stronger than aniline ($K_B = 2.7 \times 10^{-10}$) and weaker than pyridine ($K_B = 2.3 \times 10^{-9}$). The nearness of the value to that for pyridine suggests that the two benzene rings exert little influence on the central ring. Acridine forms salts with hydrochloric, nitric, and picric acids and with mercuric chloride.

---

[30] Albert and Goldacre, *J. Chem. Soc.*, 454 (1943).
[31] Jensen and Rethwisch, *J. Am. Chem. Soc.*, **50**, 1144 (1928).
[32] Barnett, Goodway, Higgins, and Lawrence, *J. Chem. Soc.*, 1224 (1934).
[33] Graebe and Caro, *Ber.*, **3**, 746 (1870).
[34] Decker, *ibid.*, **38**, 2502 (1905).
[35] Trautz, *Z. physik Chem.*, **53**, 59 (1905).

Acridine has a very stable ring system. Concentrated hydrochloric acid at 280° and fused potassium hydroxide have no action on it. Sodium dichromate in boiling acetic acid oxidizes[6,36] acridine to acridone; alkaline permanganate converts it to acridinic acid, $C_6H_4 \cdot C_3HN \cdot (CO_2H)_2$. Sodium amalgam reduces[37] acridine to 9,10-dihydroacridine. Pyrolysis[38] over catalytic nickel with hydrogen gives 2,3-dimethylquinoline. Sulfur at 200° gives thioacridone. Nitric acid forms two mono products (2- and 4-positions) and the 2,4-disubstituted product.[23,3] Halogens form addition compounds,[39] so also do the Grignard reagent[39] and acetyl chloride.[10] Alkyl halides yield quarternary salts that undergo rearrangement of the alkyl group to the 4-position.[36,11]

Acridone melts at 354° corr. and distils at higher temperatures without decomposition.[8] The yellow crystals dissolve in concentrated, but not dilute, hydrochloric or hydriodic acid and in alcoholic, but not aqueous, alkali. They are fairly soluble in hot acetic acid, but only slightly so in ether, benzene, and chloroform. Alcohol is a good solvent for crystallization

Acridone yields acridine by zinc-dust reduction[8,30 40] or by treatment with a potassium cyanide melt;[42] it gives 9,10-dihydroacridine[43] by reduction with sodium in boiling amyl alcohol; it forms 10,10′-diacridonyl,[8] $(C_{13}H_8O)N—N(C_{13}H_8O)$, by dichromate oxidation in boiling acetic acid; it changes to thioacridone[37] in poor yield, with sulfur and red phosphorus at 200°; it yields 9-chloroacridine[8] with phosphorus pentachloride and oxychloride at 120 to 130°; it forms 2,3-dibromoacridine with bromine[44] in glacial acetic acid; and it produces N-alkyl compounds[8] with alkyl iodide and the potassium salt at 130 to 140°, but not with alkyl iodide alone. In spite of the carbonyl group, no oxime nor phenylhydrazone is formed. Neither is acridone acetylated by acetic anhydride and sodium acetate.

The relative absence of basic and acidic properties, the high melting point, the absence of marked phenolic or ketonic properties, and the

---

[36] GRAEBE and CARO, *Ber.*, **13**, 99 (1880); *Ann.*, **158**, 265 (1871).

[37] EDINGER, *Ber.*, **33**, 3770 (1900); EDINGER and ARNOLD, *J. prakt. Chem.* [2], **64**, 187 (1901).

[38] PADOA and FABRIS, *Gazz. chim. ital.*, **38**, I, 283 (1908).

[39] SENIER and AUSTIN, *J. Chem. Soc.*, **85**, 1196 (1904); SENIER, AUSTIN, and CLARKE, *ibid.*, **87**, 187 (1905).

[40] TINKLER, *ibid.*, **89**, 857 (1906); KAUFMAN and ALBERTINI, *Ber.*, **42**, 2003 (1909).

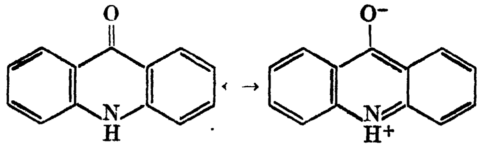
[41] DEHN, *J. Am. Chem. Soc.*, **34**, 1409 (1912).

[42] GRAEBE and LAGODYINSKI, *Ann.*, **276**, 35 (1893).

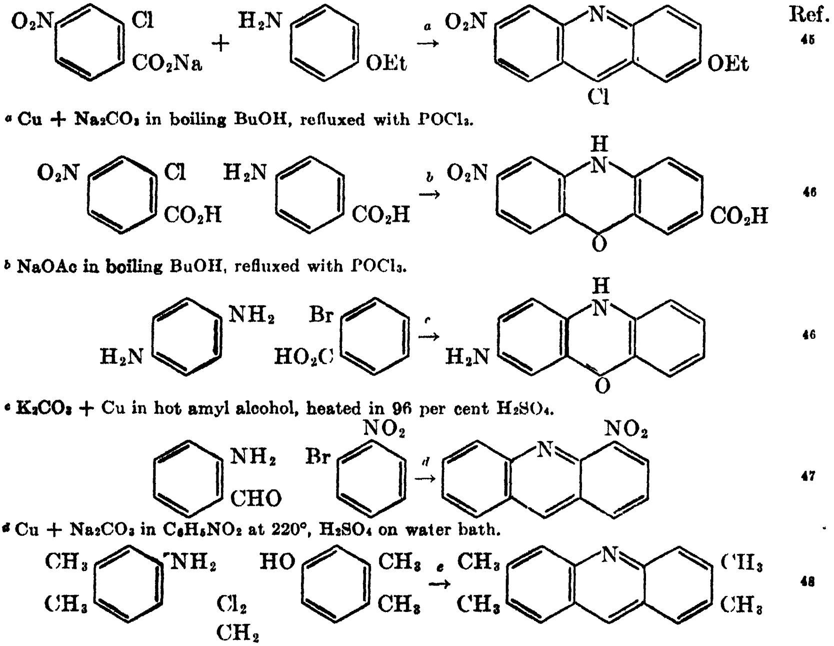
[43] ULLMANN and MAAG, *Ber.*, **40**, 2521 (1907).

[44] TANASESCU and RAMONTIANU, *Bull. soc. chim.* [5], **6**, 486 (1939).

similarity to 4-hydroxypyridine are in accordance with the view that acridone is a resonance hybrid of acridone and an unstable internal salt of 9-hydroxyacridine.[30]



Acridine or acridone compounds are invariably obtained by synthesis rather than from acridine itself. A few typical preparations are shown



ª Cu + Na_2CO_3 in boiling BuOH, refluxed with $POCl_3$.

ᵇ NaOAc in boiling BuOH, refluxed with $POCl_3$.

ᶜ K_2CO_3 + Cu in hot amyl alcohol, heated in 96 per cent H_2SO_4.

ᵈ Cu + Na_2CO_3 in $C_6H_5NO_2$ at 220°, H_2SO_4 on water bath.

ᵉ 250 to 350°.

FIG. 3.—Some methods of preparing compounds with the acridine framework.

in Fig. 3 in order to emphasize the use of anthranilic acid,[49] *o*-halogenobenzoic acids, and diphenylamine as intermediates. The halogen atom is more active if ortho to the carboxyl group or, better, ortho or para to a nitro group. The diphenylamine intermediate will form, however, when *m*-nitrobromobenzene is used.

---

[45] ALBERT and GLEDHILL, *J. Soc. Chem. Ind.*, **61T**, 159 (1942).

[46] BARNETT, GILLIESON, and KERMACK, *J. Chem. Soc.*, 433 (1934).

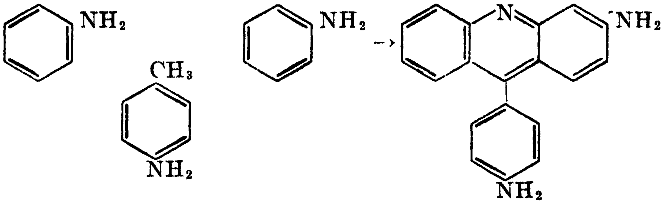
[47] JENSEN, *J. Am. Chem. Soc.*, **49**, 1049 (1927).

[48] SENIER and COMPTON, *J. Chem. Soc.*, **95**, 1623 (1914).

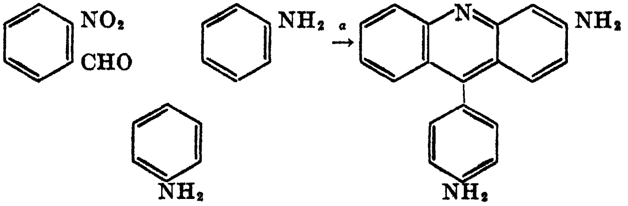
[49] HEWETT, "Dye Stuffs Derived from Pyridine, Quinoline, Acridine, and Xanthene," Longmans, Green and Company, New York, 1922.

Acridine 9-carboxylic acid (m.p. 300°d.) can be obtained[26] by treating acridylmethylol, $C_{13}H_8N.CH_2CH_2OH$ derived from 9-methylacridine and formaldehyde, with chromic–sulfuric acid on a water bath. The acid may be prepared[27] also by a longer series of reactions similar to the sequence used for converting 4-methylquinoline to quinoline-4-carboxylic acid (page 285). 9-Methylacridine condenses with chloral, aqueous 20 per cent alkali causes hydrolysis and loss of water, permanganate oxidizes the resulting acrylic acid, and silver oxide and alkali then convert the aldehyde to acridine-9-carboxylic acid. Like other sterically hindered acids, this compound cannot be esterified by alcohol and mineral acids. Conversion to the chloride and thence to the methyl or ethyl ester gives products melting at 127.5 or 78°, respectively.

Acridine Dyes.—The first acridine dye[49] came as a by-product in the preparation of fuchsin by oxidation of a mixture of *p*-toluidine and aniline with arsenic acid or nitrobenzene. One of the aniline molecules condenses in the ortho instead of the para position. The product is known as Chrysaniline or Phosphine and has received considerable attention as a yellow dye for leather.



Though discovered in 1863 by Nicholson, its structure was not determined until 21 years later, when Fischer and Körner[50] converted it to 9-phenylacridine by eliminating the amino groups with the aid of the diazonium reaction and confirmed their conclusion by a synthesis from *o*-nitrobenzaldehyde and aniline. The free base melts at 265°. The nitrate or hydrochloride is used as the dye.



[a] The nitrobenzaldehyde is first condensed with two molecules of aniline sulfate in the presence of zinc chloride. From the resinous mass a product is obtained, which, by reduction with zinc dust and acid, forms triaminotriphenylmethane. Arsenic acid at 180–200° then forms the dye.

---

[50] Fischer and Körner, *Ber.*, **17**, 207 (1884).

The important acridine dyes are, in general, derived from *m*-phenylenediamine, 2,4-dinitrotoluidine, their equivalents or their derivatives. Methods[51] that illustrate the preparation of several of these compounds are given in Fig. 4.

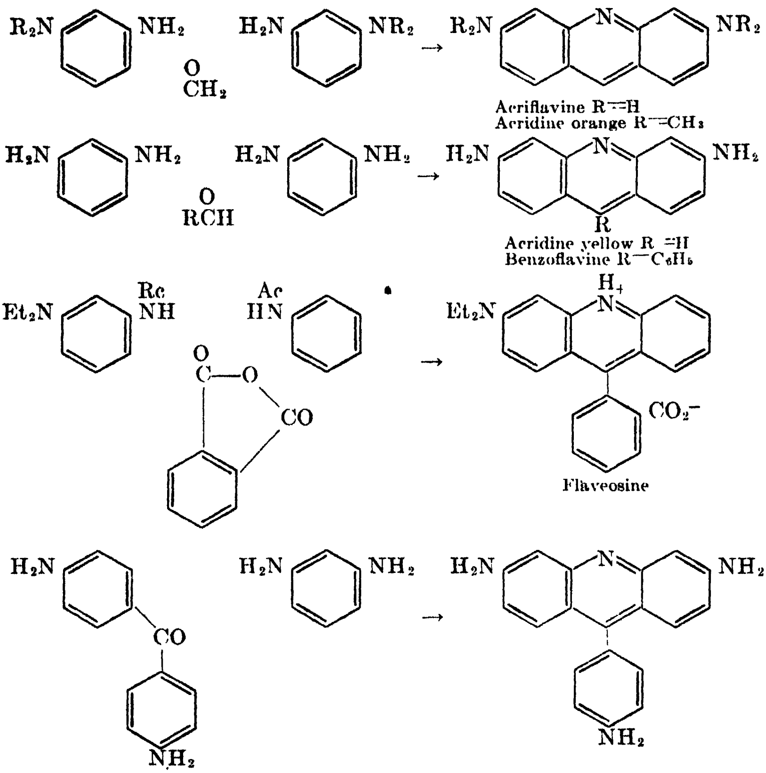


FIG. 4.—Methods for the preparation of some acridine dyes.

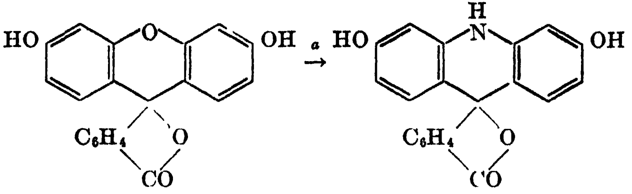
An alternative preparation of acriflavine is accomplished by nitration of 4,4′-diaminodiphenylethane, reduction of the nitro groups with tin and hydrochloric acid, thermolysis of the tin salt product at 135°, and oxidation of the acridane with ferric chloride.

In addition to the many processes like those above, there are several preparations that illustrate interesting chemical reactions or lead to variations in the types of dyes. For instance, the replacement of oxygen by nitrogen, mentioned often in this text, takes place with fluorescein and gives an acridine,[52] which becomes a dye when treated with an alkyl halide or an alcohol and acid. Cleavage of a carbon-carbon bond results when a tetraminoditolylmethane[53] is heated with β-naphthol. Addition to an anil of *p*-nitrobenzaldehyde leads eventually to an acridine compound.[54] These changes are shown below.

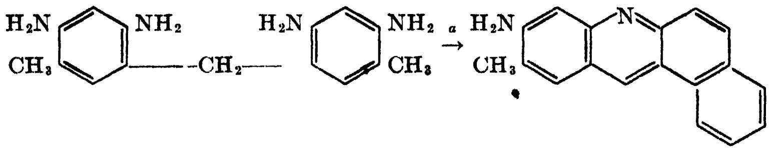
---

[51] BENDA, *ibid.*, **45**, 1787 (1912); EHRLICH and BENDA, *ibid.*, **46**, 1933 (1914); SCHOPFF, *ibid.*, **27**, 2317 (1894); SMEROUS, *Ann.*, **414**, 181 (1918).

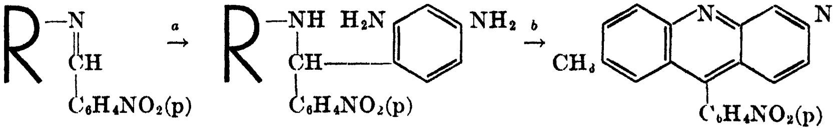
[52] MEYER and OPPELT, *Ber.*, **21**, 3376 (1888).



a NH_3.

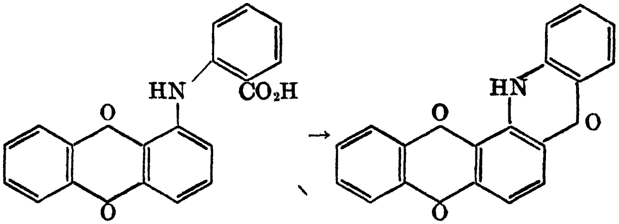


a Reaction with β-naphthol. Elimination of 2,4-diaminotoluene.



Large R = p-$CH_3C_6H_4$.
a Addition of *m*-phenylenediamine to the anil.
b Ring closure.

Combination with anthraquinone gives a dye that has the advantages of vat dyeing.[55] The intermediate anthraquinone-1-anilino-*o*-carboxylic acid is obtained from 1-aminoanthraquinone and anthranilic acid. Bis- as well as mono-acridylanthraquinone compounds have been so prepared.



The bis product so prepared from 1,5-dichloroanthraquinone is known as indanthrene violet BN. It is not a true indanthrene but is a benzo[1,2-c,4,5-c′]diacridine.

Dyes of the acridine type color cotton and leather. Acridine orange is used as a photographic sensitizer[56] in company with other anilinium

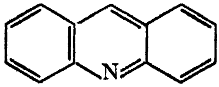
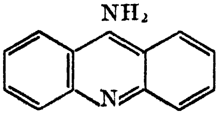
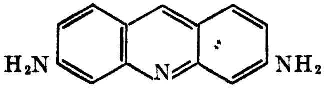
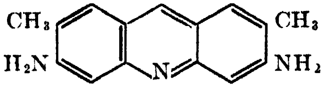
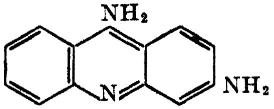
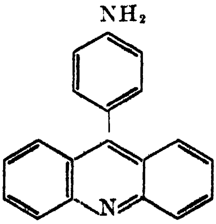
[53] Ullmann and Neff, *ibid.*, **33**, 914 (1900); *cf.* British patent 16,474 (1888).

[54] D.R.P., 106,719 (1898).

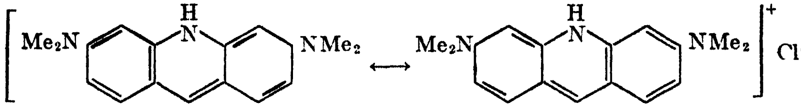
[55] Ullmann and Uchsner, *Ann.*, **381**, 1 (1911); Ullmann and Dootson, *Ber.*, **51**, 9 (1918).

[56] Mees, "The Theory of the Photographic Process," The Macmillan Company, New York, 1942.

TABLE I.—ACRIDINE COMPOUNDS WITH ANTISEPTIC ACTIVITY

Structural formula; principal type.	Name of principal type; names of substituents present	Trade name
	Acridine	Acridine
	Methochloride of 3,6-dimethoxy-	Sinflavine
	9-Aminoacridine	
	Dihydrochloride of 3,6-dimethoxy-	
	3,6-Diaminoacridine	
	Sulfate	Proflavine
	Hydrochloride	Flavine or trypaflavine
	Methochloride	Acriflavine, trypaflavine neutral, or euflavine
	Methiodide	Iodoflavine
	N,N-Tetramethyl-	Acridine orange .
	2,7-Dimethyl-3,6-diaminoacridine	Acridine yellow
	Methonitrate	Brilliant phosphine yellow
	Methochloride of N-methyl-	
	Methochloride of N-dimethyl-	Flavicide
	Methonitrate of N-dimethyl-	Brilliant phosphino immino
	6,9-Diaminoacridine	
	Lactate of 2-ethoxy-	Rivanol
	9 (4'-aminophenyl)-acridine	
	Hydrochloride of 2-amino-	Diaminophosphine, chrysaniline
	Hydrochloride of 6-methyl-2-amino	Monomethylphosphine
	3,6-Dimethyl-2-amino-	Dimethylaminophosphine, benzoflavine

ion systems such as rhodanine, pinacyanol, or pinaflavol. The color is caused by the fact that resonance exists between nitrogen atoms that have similar basicity. Two structures are shown below.



The *therapeutic activity* of acridine compound[57] was discovered by Ehrlich and coworkers during studies with triphenylmethane dyes. Crude dichloro ortho-para fuchsin proved less toxic but more trypanocidal than para fuchsin, methyl violet, and like compounds. The difference was traced to the presence of an impurity, an acridine compound, the formation of which has already been discussed. Acridine, itself, has only a little activity; but the amino-substituted compounds, particularly the 2,6-diamino substituted acridines, have attracted much attention.[58] A number of comparatively simple compounds, which have an antiseptic action on paramecia, gonococci, and pneumococci are listed in Table I.

In general, the introduction of amino and, to a less extent, of methyl groups increases antiseptic action.[58] Change of the ring nitrogen atom from a trivalent state to the ammonium salt increases the effectiveness. The methiodide salt, iodoflavine, is about half as active as the corresponding methochloride, acriflavine. The antiseptic action of these compounds is probably affected greatly by the dispersion of the drug. Light has a pronounced effect.

The most active of the compounds listed are acriflavine (trypaflavine) and rivanol. The name "trypaflavine" was given by Ehrlich because of its trypanocidal powers and its yellow color. The English called the compound "acriflavine." While not a remedy for trypanosomiasis, the compound received considerable attention during the First World War because of its effect on bacterial wound infections. It has been used as a urinary antiseptic,[59a] but other compounds have supplanted it.

Table II shows the relationship of basic strength, determined in 67 per cent methanol, to the bacteriostatic index of the aminoacridines.[30] Values for the bacteriostatic effect are expressed in powers of 2. Hence 9-aminoacridine is $2^{3.8}$, or fourteen, times as effective as 4-aminoacridine. The high basicities of the 9-amino and 3-amino compounds are consonant

---

[57] BENDA, "Chemotherapeutic Acridine Compounds," Reports from the Medico Chemical Research Laboratories of the I. G. Farbenindustrie, Leverkusen, Germany.

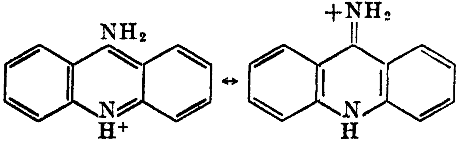
[58] v. OETTINGEN, "Therapeutic Agents of the Quinoline Group," Reinhold Publishing Corporation, New York, 1933.

[59] (*a*) GOODWIN and GILMAN, "The Physiological Basis of Therapeutics," The Macmillan Company, New York, 1941. (*b*) See Ref. 30 and KUMLER and DANIELS, *J. Am. Chem. Soc.*, **65**, 2194 (1943).

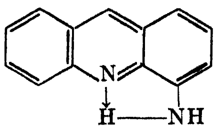
TABLE II.—BASIC STRENGTH AND BACTERIOSTATIC ACTIVITY OF SOME AMINOACRIDINES

Acridine substituent	K_B	B
None	3×10^{-10}	1.2
4-Amino	4×10^{-11}	0.8
2-Amino-	2×10^{-9}	1.6
1-Amino-	5×10^{-9}	1.8
3-Amino-	3×10^{-7}	4.2
9-Amino-	2×10^{-5}	4.6

with the resonance effect.[59b] The low value for 4-aminoacridine suggests hydrogen bonding.

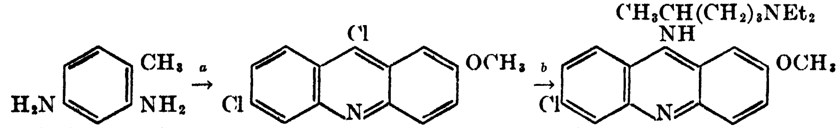


9-Aminoacridine



4-Aminoacridine

Atebrin is 3-chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)-acridine dihydrochloride. The nonproprietary name is quinacrine hydrochloride. Synthesis consists of preparing the acridine and amine portions separately and then uniting the two parts. Methods



[a] Replacement of the amino groups by chloro atoms by means of nitrous acid and cuprous chloride, oxidation of the methyl group by permanganate, condensation with *p*-anisidine by reaction with one of the chloro atoms, ring formation with phosphorus oxychloride. [b] Reaction with the amine, $NH_2CH(CH_3)(CH_2)_2CH_2NEt_2$, in an anhydrous phenol melt. The amine is prepared from ethyl acetoacetate by alkaline condensation with ethylene oxide, followed by reactions with hydrogen bromide, diethyl amine, hydroxyl amine, and sodium and alcohol. Instead of the ethylene oxide, hydrogen bromide, and diethylamine, the condensation with $ClCH_2CH_2NEt$ may be used; and in place of the oxime-sodium and alcohol steps, the ketone may be catalytically reduced in the presence of ammonia.

FIG. 5.—Preparation of atebrin.

are shown in Fig. 5. The compound melts at 245 to 255° and has considerable value as an antimalarial. Production reached enormous quantities[60] during the Second World War.

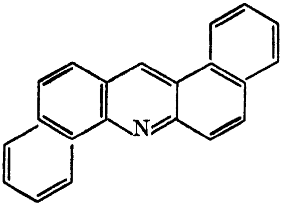
Rubber inhibitors have been made from compounds[61] in the acridine series. 9,9-*Dimethylacridine*, from acetone, diphenylamine, and zinc chloride, is claimed to be an antioxidant for vulcanized rubber. It probably owes whatever value it has to its relation to the comparatively active diphenylamine.

---

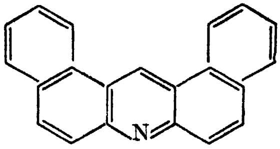
[60] SHERNDAL, *Chem. Eng. News*, **21**, 1154 (1943).

[61] HORST, U.S. patent 1,915,108 (1933); SEMAN, Canadian patent 337,506 (1933); SCOTT, U.S. patent 1,958,928 (1934); SHEPARD, *Ind. Eng. Chem.*, **28**, 281 (1936).

Naphthacridines.—These high molecular weight acridines have received some attention because the framework of one is similar to that of 1,2,5,6-dibenzanthracene, the cancer-producing compound. Both the compounds[62] above cause cancer. The respective syntheses[63] are effected by the thermal condensation at 160° of α-naphthylamine and β-naphthol with formaldehyde at 160° and of β-naphthylamine and β-naphthol with formaldehyde at 200°. The compounds melt at 228 and 216°, respectively.



1,2,5,6-Dibenzacridine or dibenz[*a,h*]acridine



1,2,7,8-Dibenzacridine or dibenz[*a,j*]acridine

Phenanthridines.—Phenanthridines have received less attention than acridines because they have no commercial importance. A standard preparative method is to treat *o*-acyl- or *o*-aroyl-amino substituted biphenyls with fused zinc chloride at 250 to 300° or better with phosphorus oxychloride.[64] Pyrolysis of benzanilide[7] or of benzalaniline[65] also gives phenanthridine. Benzalaniline was, in fact, the first source of phenanthridine. In addition, there are a number of rearrangements of fluorene or indole compounds (see Fig. 6) that yield phenanthridines or phenanthridones. The first one[66] is a utilization of the common instability of the nitrogen-chlorine system coupled by a ring strain in the fluorene framework; the second[66] is somewhat similar, but with the unstable azide group; the third[67] is the conventional Beckmann change, which in the case of this nitrofluorenone oxime occurs in such way that the two nitrogen atoms take positions as far apart as possible (the same result is realized in the Curtius degradation[68] of the hydrazide of 4-nitrodiphenic acid); and the fourth[69] is a pyrolysis method that is of the same type as the change of α-methylpyrrole to pyridine, of N-benzylpyrrole to β-phenylpyridine, of α-methylindole to quinoline, or of α-methylisoindole to isoquinoline.

[62] Barry, Cook, *et al.*, *Proc. Roy. Soc. London*, Sec. B, **117**, 331 (1935).

[63] Ullmann and Fetvadgian, *Ber.*, **36**, 1027 (1903); Möhlau and Hasse, *ibid.*, **35**, 4164 (1902).

[64] Morgan and Walls, *J. Chem. Soc.*, 2447 (1931).

[65] Pictet and Ankersmit, *Ber.*, **22**, 3339 (1889); *Ann.*, **266**, 138 (1891).

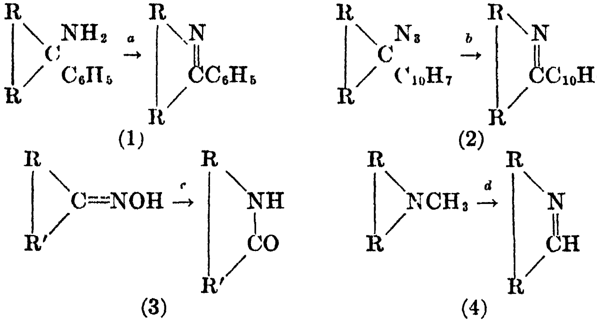
[66] Pinck and Hilbert, *J. Am. Chem. Soc.*, **59**, 8 (1937).

[67] Moore and Huntress, *ibid.*, **49**, 1324, 2618 (1927).

[68] Labriola and Felitte, *J. Org. Chem.*, **8**, 536 (1943).

[69] Pictet, *Ber.*, **38**, 1946 (1905).

Phenanthridine (m.p. 104°, b.p. above 360°) and *phenanthridone* (m.p. 293°) have, in general, the properties that would be expected from the similarity to the corresponding acridine compounds and from the presence of a pyridine ring. Phenanthridine is unaffected by chromic-acetic acid mixture, but is oxidized[70] by calcium hypochlorite and cobalt nitrate. The phenanthridone product, in turn, reverts[65] to phenanthridine when heated with zinc dust. Tin and hydrochloric acid, but not iron and acidified water, reduce phenanthridine to 5,6-dihydrophenanthridine. Hence nitrophenanthridines can be reduced to amino compounds by iron and acid without the nucleus being affected.[64] Sodamide in xylene at 120 to 130° produces an almost quantitative yield of 6-aminophenanthridine from phenanthridine. The amino group, as expected, hydrolyzes slowly and does not undergo diazotization in acid solution. The monoacetylated product yields no salt when treated with methyl sulfate.



R = C_6H_4; R′ = $O_2NC_6H_3$.

[a] 9-Phenyl-9-aminofluorene, prepared from the corresponding chloro compound and ammonia, is treated with sodium hypochlorite and then with anhydrous pyridine and sodium methoxide. [b] The azide, prepared from 9-naphthyl-9-chlorofluorene by treatment with hydrazine and then with nitrous acid, is converted by heat to the phenanthridine. [c] The oxime, prepared by treatment of 4-nitrodiphenic acid with concentrated sulfuric acid, is treated with phosphorus pentachloride in order to form the phenanthridone. [d] The methylcarbazole, prepared from potassium carbazole and methyl iodide, is passed through a tube, heated to dull redness.

FIG. 6.—Methods for preparing phenanthridines and phenanthridones from fluorene compounds by rearrangements.

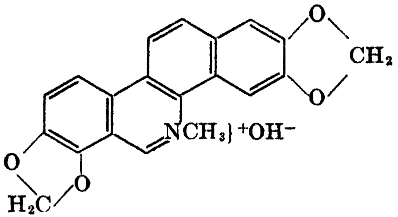
Chelidonine, sanguinarine, and chelerythrine are alkaloids of the 3,4-benzphenanthridine type. The probable structure[71] of sanguinarine is shown below; that of chelerythrine is similar except for two methoxy groups in place of the methylene dioxy group in the isoquinoline portion of the molecule. Synthesis[72] of the framework of compounds of this

---

[70] PICTET and PATRY, *ibid.*, **26**, 1964 (1903).

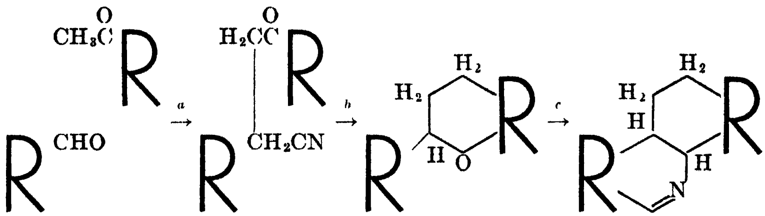
[71] SPÄTH and KUFFNER, *ibid.*, **64**, 1123, 2034 (1931).

[72] RICHARDSON, ROBINSON, and SEIJO, *J. Chem. Soc.*, 835 (1937).



Sanguinarine

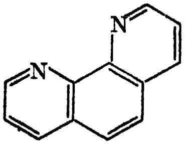
type (but not of the alkaloid itself) is illustrated below. The process is an application of Pschorr's phenanthrene synthesis. The large R represents a dimethoxyphenyl or dimethoxybenz system, and the two starting reagents are veratraldehyde, 1,2,4-$(CH_3O)_2C_6H_3CHO$, and acetoveratrone, 1,2,4-$(CH_3O)_2C_6H_3C(O)CH_3$. The steps are conventional ones; the nitrile is obtained by addition of hydrogen cyanide to the chalcone; the nitrile is hydrolyzed to the acid, the ketone is reduced and the ring



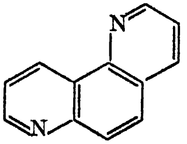
[a] Aqueous NaOH, NaCN in HOAc. [b] Concentrated H_2SO_4, boiling NaOH, Zn + HCl in HOAc, $POCl_3$. [c] H_2NOH, Na + C_3H_7OH, anhyd. HCO_2H, $POCl_3$.

closed in the second series; the formylated amine undergoes ring closure (isoquinoline formation) in the third series. An alternative to the last set of four reactions is to heat with formamide and then treat with phosphorus oxychloride.

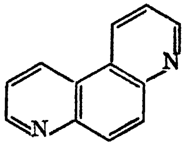
Phenanthrolines.—Compounds in which two pyridine rings are fused to one benzene ring in an angular arrangement are known as phenanthrolines. Theoretically, they are derived by a simultaneous double Skraup synthesis from *o*-, *m*-, and *p*-phenylenediamine (see below) and hence are often called *o*-, *m*-, and *p*-phenanthroline; actually only the *m*-



M.p. 117°



78–78.5°



177°

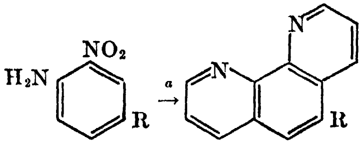
and *p*-phenanthrolines can be so prepared.[73] The ortho isomer—and, of course, the other two, if desired—can be prepared by a succession of

---

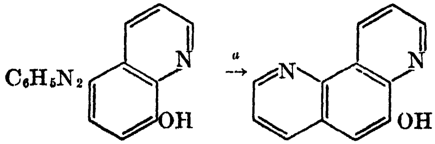
[73] Kaufmann and Radošević, *Ber.*, **42**, 2613 (1909).

Skraup syntheses, first on the nitroaniline and, second, on the reduction product of the nitroquinoline first formed. Ring closure invariably forms an angular product.[74]

Substituted phenanthrolines can be obtained[75] from appropriately substituted aniline compounds as shown below. They may also be prepared from benzene azo compounds[76]—a source particularly valuable when the amino compound is unstable or difficult to obtain. For example, 5-benzeneazo-8-hydroxyquinoline gives hydroxy-*m*-phenanthroline, and *p*-aminoazobenzene gives *p*-phenanthroline in good yield.



[a] Skraup synthesis, reduction with Sn + HCl or with Fe + HCl, Skraup synthesis. Melting points of products are 123, 119, and 114° as R is Cl, Br, or CH_3, respectively.



[a] Skraup synthesis.

o-Phenanthroline forms a red complex with ferrous chloride, known as "ferroin,"[77] which is an exceptionally good reversible indicator for electrometric processes.[78] The ferric salt is blue. The molal potential is 1.14 volts. It can be used with such oxidizing agents as ceric sulfate, potassium permanganate, and potassium dichromate. The nitro derivatives have higher oxidation potentials.[77] *o*-Phenanthroline has also received some attention as a bacteriological stain and, in the form of the cobalt and manganese complexes, as a drying agent.[79]

The *m*- and *p*-phenanthrolines are oxidized by alkaline permanganate to dipyridyldicarboxylic acids, and the diacids, in turn, are converted to dipyridyls by heat. In the case of the α,β'-diacid, one of the carbonyl groups is lost at 200°, the other one at a higher temperature. The oxidation processes are preparative ones for α,β- and β,β-dipyridyls.[80] Two examples will be given. *p*-Phenylenediamine condenses almost quantitatively with 2 molecules of ethyl acetoacetate, and the β-amino product undergoes ring closure when heated in paraffin oil at 260° after the well-known process for preparing 4-hydroxy lepidines. Oxidation of the phenanthroline product (m.p. 332°) gives a dipyridyldicarboxylic acid.[81]

---

[74] Two notable exceptions to the rule that angular products always result from Skraup synthesis are (*a*) the linear product from 1-chloro-2-naphthylamine (see page 395), and (*b*) the angular and linear products from 2-aminotetralin. This last compound, however, is more like an alkylaminobenzene than a true naphthalene derivative. Hence condensation should, and does, occur on both sides of the amino group. [v. Braun and Gruber, *Ber.*, **55**, 1710 (1922).]

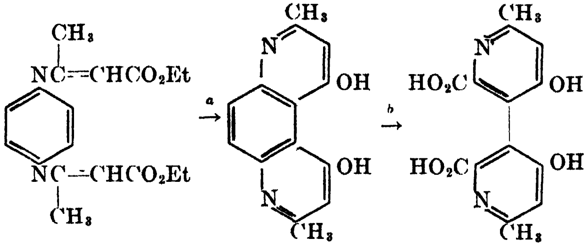
[75] Richter and Smith, *J. Am. Chem. Soc.*, **66**, 396 (1944).

[76] Matsumura, *ibid.*, **52**, 3974 (1930).

[77] Smith and Getz, *Chem. Rev.*, **16**, 113 (1935).

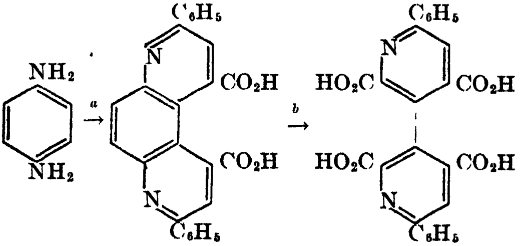
[78] Walden, Hammett, and Chapman, *J. Am. Chem. Soc.*, **53**, 3908 (1931).

[79] Nicholson, *Ind. Eng. Chem.*, **34**, 1175 (1942).



^a Heat at 260°. (A Conrad-Limpach reaction) ^b $KMnO_4$.

In the second example, a double pyruvic acid condensation, so useful in the preparation of quinolines, is applied to *p*-phenylenediamine. The phenanthroline is oxidized to 2,4,2′,4′-tetracarboxy-6,6′-diphenyl-3-3′-dipyridyl. This last compound was prepared in connection with studies on restricted rotation. The dipyridyl exists in two stereoisomeric forms, but the interference to rotation is less than in the diphenyl series.[82]



^a Dobners pyruvic acid condensation with benzaldehyde. ^b $KMnO_4$.

Anthrazolines.—When two pyridine rings are fused to the same benzene ring in a linear arrangement, the products are known as anthrazolines. The compounds are more difficult to prepare than the phenanthrolines, since the Skraup synthesis can no longer be used. Preparation of 1,9-anthrazoline[83] (the compound can be called also pyrido[3,2-*g*] quinoline and diazanthracene) from 4,6-dimethyl-1,3-dinitrobenzene is shown below.

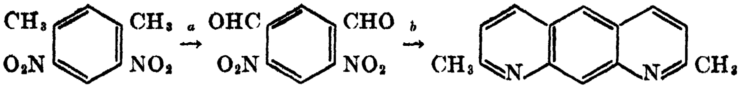
---

[80] SMITH, *J. Am. Chem. Soc.*, **52**, 397 (1930).

[81] JACINI and BERTULLI, *Gazz. chim. ital.*, **69**, 111 (1939); *C.A.*, **33**, 5402 (1939); JACINI and SALINI, *Gazz. chim. ital.*, **69**, 717 (1939); *C.A.*, **34**, 4737 (1940).

[82] WOODRUFF and ADAMS, *J. Am. Chem. Soc.*, **54**, 1977 (1932).

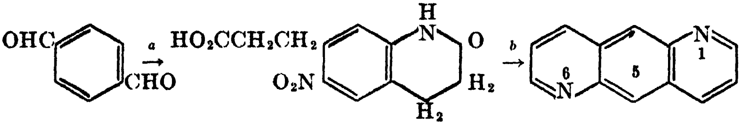
[83] RUGGLI, HINDERMANN, and FREY, *Helv. Chim. Acta*, **21**, 1066 (1938).



[a] p-$QNC_6H_4N(CH_3)_2$, $H_2O + HNO_3$. [b] $FeSO_4 + NH_3$, $CH_3C(O)CH_2CO_2Et$, KOH, HCl, heat. The two methyl groups can be removed from the product by bromination, followed by acid hydrolysis and decarboxylation.

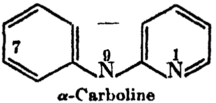
Compounds in this series have the properties expected from the behavior of less complex molecules. The two methyl groups in 2,8-dimethylanthrazoline are like the methyl groups in quinaldine; and sodium and hot amyl alcohol reduce anthrazoline to a 1,2,3,4,6,7,8,9-octahydro product.[84]

Synthesis of the 1,6-anthrazoline (or pyrido[2,3-*g*]quinoline) is accomplished[85] by a longer sequence of reactions that begins with terephthaldehyde.

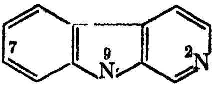


[a] Nitration introduces one nitro group, malonic acid condensation, decarboxylation, catalytic reduction over Raney nickel, nitration with nitric-sulfuric acid. [b] $H_2 + Ni$, $POCl_3 + PCl_5$, HI + P in CH_3CO_2H at 150 to 173°.

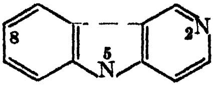
Pyridindoles or Carbolines.—The structure of the pyrindoles is that of a pyridine fused with an indole system. Because they have the appearance of a carbazole and a quinoline, they are frequently called carbolines.[86] According to the "The Ring Index,"[1] the compounds are named as pyridindoles and numbered as shown below. The name



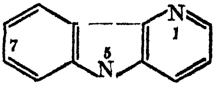
α-Carboline
9-Pyrid[2,3-*b*]indole



β-Carboline
9-Pyrid[3,4-*b*]indole



γ-Carboline
5-Pyrid[4,3-*b*]indole



δ-Carboline
5-Pyrid[3,2-*b*]indole

"carboline" is more convenient in some respects than pyridindole, but considerable confusion exists in the literature as to how the isomeric carbolines shall be designated. This text employs the prefixes—α, β, γ, and δ to indicate the position of the nitrogen atom in the pyridine ring relative to that in the indole system and uses the general system of numbering as given in "The Ring Index" to indicate the position of a substituent.

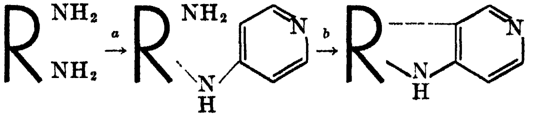
---

[84] Ruggli and Frey, *ibid.*, **22**, 1413 (1939).

[85] Ruggli and Preiswerk, *ibid.*, **22**, 478 (1939).

[86] Perkin and Robinson, *J. Chem. Soc.*, **115**, 967 (1919).

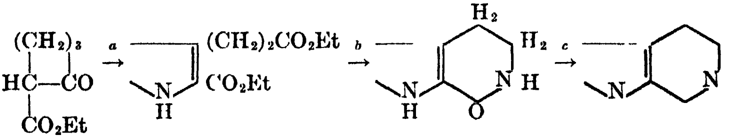
The α- or γ-carbolines are prepared readily from α- or γ-chloropyridines and *o*-phenylenediamine[87] by the method illustrated below for the γ-isomer.



[a] γ-Chloropyridine. [b] HNO_2, hot H_3PO_4 in order to decompose the triazole and form the carboline. Fused zinc chloride is used in the formation of the α-isomer.

More complicated compounds of this type can be prepared from α- and γ-chloroquinoline by means of the same reaction. The process is identical with that for making carbazoles.

The β-carboline framework is found in some alkaloids. In the laboratory, it can be obtained by the method shown below for the synthesis of norharman.[88] The first step is a fine example of the Japp-Klinglemann reaction. Ethyl cyclopentanone carboxylate behaves as do the substituted ethyl acetoacetates (page 102) in which the indole is formed with extrusion of the ketone group. The ethyl β-(indoxyl-3)-propionate product (this method is an excellent one for obtaining this ester) is converted to the azide, which, in turn, is heated according to the conventional practice for forming isocyanates. Ring closure simultaneously takes place. Save for a poor yield in the last step, the procedure is good.



[a] The ethyl cyclopentanone carboxylate is shaken with a suitable phenyldiazonium chloride and the product is refluxed with alcoholic sulfuric acid. [b] Hydrolysis, decarboxylation, and esterification followed by treatment with hydrazine hydrate, sodium nitrite in acetic acid, and heat in boiling benzene. [c] Zinc dust distillation. Partial formulas are used in the above diagrams.

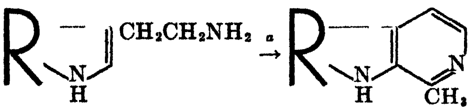
A better method[89] employs the well-known process for making isoquinolines, as shown below for harman.

---

[87] Robinson and Thornley, *ibid.*, 2169 (1924); Lawson, Perkin, Jr., and Robinson, *ibid.*, 626 (1924).

[88] Manske and Robinson, *J. Chem. Soc.*, 240 (1927); *cf.* Kalb, Schweitzer, and Schimpf, *Ber.*, **59**, 1858 (1926).

[89] Späth and Lederer, *Ber.*, **63**, 120 (1930).



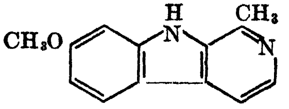
[a] Acetic anhydride, phosphorus pentoxide, palladium black at 195°.

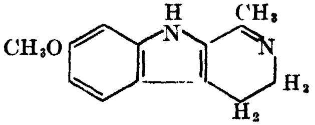
The related biological process, in which tryptamine condenses with acetaldehyde at room temperature in a buffered solution (P_H = 5 or 6),[90] gives an almost quantitative yield of tetrahydroharman.

Occurrence of the β-carboline nucleus in alkaloids such as harmine or yohimbine is probably related to the presence of tryptophan in nature.

Harmine and Related Alkaloids.—The seeds of *Paganum harmala*, a plant found in the South Russian steppes and in India, are used in Turkey as a vermifuge and in India as a disinfectant and a red dye. The chief alkaloids[91] present are harmine, $C_{13}H_{12}N_2O$, harmaline, $C_{13}H_{14}N_2O$, and harmalol, $C_{12}H_{12}N_2O$. Harmine is probably present also in the South American plant "yage" or "caapi," used by the natives in preparing an intoxicant. Remarkable properties have been ascribed to harmine under the name of "yageine," "banisterine," and "telepathine." In large doses, harmine causes tremors and convulsions.

Formulas for harmine and harmaline are shown below.





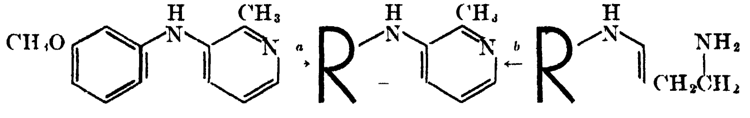
In harmalol, the methoxy group of harmaline is replaced by a hydroxyl group. Degradation and other studies[92] show that the alkaloids contain (*a*) an active methyl group that condenses readily with benzaldehyde to give a benzylidene derivative, which, by permanganate oxidation and decarboxylation of the resulting acid in hot glycerol, is converted to norharman (the prefix *nor*- means "methyl-free"); (*b*) a methoxybenzene ring that survives, in the form of *m*-nitroanisic acid, the nitric acid oxidation of harmaline; (*c*) a pyridine ring, which, after oxidation of harmin with chromic acid, appears as harminic acid, $C_8H_6N_2{\cdot}COOH$, which, in turn, changes to isonicotinic acid by further oxidation with nitric acid; (*d*) an unsubstituted nitrogen atom that is methylated by methyl iodide, or acetylated by acetic anhydride; and (*e*) an absence of any carbon atom attached to the β-position of the pyridine ring because the product of oxidative degradation shows no β-acid under conditions where the less stable *p*-carboxyl group survives. Furthermore, dilute nitric acid oxidizes harmaline to harmine, and reduction of either compound gives tetrahydroharmin; both reactions are typical of a pyridine ring. Consideration of these facts suggests a fused phenyl, pyrrole, and pyridine system in the order named. Indeed, the base, harman, derived by elimination of the methoxy group, is identical with the base derived from tryptophan by oxidation with ferric chloride in the presence of alcohol or by treatment with acetic anhydride and zinc chloride followed by oxidation with dichromate.

---

[90] HAHN and LUDEWIG, *Ber.*, **67**, 2031 (1934).

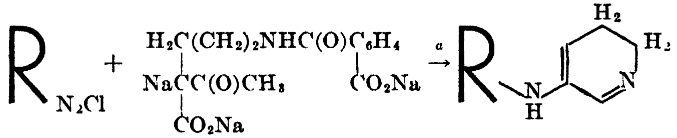
[91] HENRY, "The Plant Alkaloids," 3d ed., The Blakiston Company, Philadelphia, 1939.

[92] PERKIN and ROBINSON, *J. Chem. Soc.*, **101**, 1775 (1912); **115**, 933, 967 (1919).



Large R = $C_6H_4<$.
[a] HCl at 140 to 150°, $ZnCl_2 + NH_3$ at 250°, HNO_2 [b] CH_3CHO, $FeCl_3$ or $Ac_2O + ZnCl_2$, $K_2Cr_2O_7$.

Synthesis of *harmalan*,[93] the methoxy-free compound corresponding to harmaline, is effected by a sequence of indole and piperidine preparations. Benzenediazonium chloride reacts with a sodium sodioacetoacetate derivative. Because the sodium salt is used in place of the ester, the carboxyl, rather than the acetyl, group is extruded during the coupling process (the ketone group is extruded in the preparation of norharman, page 347). The remaining steps are common.



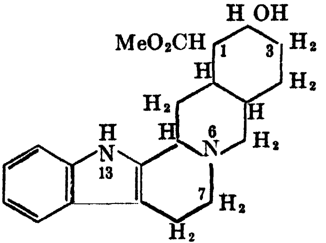
[a] The chain attached to acetoacetic acid is obtained with trimethylene bromide and potassium phthalimide. The Japp-Klinglemann synthesis causes extrusion of the carboxyl group (see page 102), acetic anhydride causes the phthalimide ring to form, dry hydrochloric acid forms the indole system, hydrazine hydrate and hydrolysis remove the phthalic acid (see page 115), dry hydrochloric acid forms the pyridine ring.

Harman (m.p. 235.5°) occurs in nature as the alkaloids aribine and loturine.[94] Harman, norharman, indole carboxylic acid, and other bases have been isolated also among the products of alkali fusion of the alkaloids, alstonine and tetrahydroalstonine, obtained from alstonia. These alkaloids, but not the derived bases, have some antimalarial activity.[95]

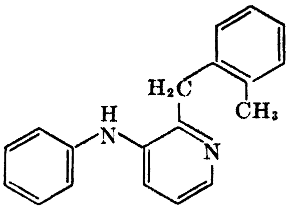
Yohimbine, $C_{21}H_{26}N_2O_3$, is an alkaloid from the yohimbé bark, used by West African natives as a powerful aphrodisiac. It is identical with quebrachine from the bark of the quebracho tree in Argentina.

[93] Manske, Perkin, and Robinson, *ibid.*, 1 (1927).
[94] Späth, *Monatsh.*, **40**, 351 (1919); **41**, 401 (1920).
[95] Leonard and Elderfield, *J. Org. Chem.*, **7**, 556 (1942).

Degradation studies[96] suggest the structures[97] shown below.



Yohimbine



Yobyrin

Alkaline saponification gives yohimbic acid. Oxidation of the decarboxylated product converts the secondary alcohol to a ketone. Pyrolysis (dry distillation of acid or ester with soda lime or zinc dust, distillation with superheated steam at 300°) gives fragments such as 3-ethylindole, indole-2-carboxylic acid, harman, and isoquinoline. Selenium dehydrogenation gives yobyrin, $C_{19}H_{16}N_2$, tetrahydroyobyrin, $C_{19}H_{20}N_2$, and ketoyobyrin, $C_{20}H_{16}N_2O$. Nitric acid oxidizes the tetrahydro product to berberonic acid, which is 2,4,5-pyridinetricarboxylic acid. Gentle alkali fusion (KOH in boiling amyl alcohol for 12 hr.) of the keto compound gives norharman and 2,3-dimethylbenzoic acid.

The carbomethoxy group may, however, be at C_7 instead of C_1. A solution of yohimbine behaves toward concentrated sulfuric acid and an oxidizing agent ($FeCl_3$) as does 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid. A play of colors from green to yellow, orange, red, and violet occurs at the interphase of the solutions. The reaction is the Adamkiewicz test for tryptophan, which apparently depends on the formation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, since only those compounds that have or can form such a product give the test.[98] The fact that yohimbine gives the test suggests that the carbomethoxy group is at C_7.

The Ergot Alkaloids.—Ergot is a fungus that grows on rye. In years past, countries, chiefly central European, that depended on rye as a staple food were frequently subjected to frightful epidemics of gangrene,[99] caused by this fungus. Since 1860, no outbreak of the disease has been reported.

The amount of mixed alkaloids in the ergot does not exceed 0.1 per cent. Simple bases, such as histamine, tyramine, cadaverine, and putrescine, are present in the extract. Some of the complex alkaloids, such as ergotoxime, $C_{35}H_{41}N_5O_6$, ergotamine, $C_{33}H_{35}N_5O_5$, and particularly ergonovine (also called ergobasine, ergometrine, ergostetrine, and ergotocine) $C_{19}H_{23}N_3O_2$, are very important physiologically because they induce rhythmic contraction of the puerperal uterus. Isomeric and interconvertible with these compounds are the physiologically inert alkaloids, ergotinine (the formula is identical with ergotoxime save for the absence of water of crystallization), ergotamine, and ergometrimine, respectively.

---

[96] BARGER and SCHOLZ, *J. Chem. Soc.*, **614** (1933); *Helv. Chim. Acta.*, **16**, 1343 (1933); CLEMO and SWAN, *J. Chem. Soc.*, 617 (1946).

[97] HAHN, KAPPES, and LUDEWIG, *Ber.*, **67**, 686 (1934).

[98] HARVEY, MILLER, and ROBSON, *J. Chem. Soc.*, 153 (1941).

[99] BARGER, "Ergot and Ergotism," Gurney and Jackson, London, 1931.

The ergot alkaloids appear to be combinations of lysergic acid, or its isomer, with certain amino acids or compounds derived from them, such as 2-aminopropanol-1, pyruvic acid, or isobutylformic acid.[100] Methyl alcoholic potassium hydroxide converts the four large molecular weight alkaloids to ergine,[101] $C_{16}H_{17}N_3O$, the amid of lysergic acid, $C_{16}H_{16}N_2O_2$; aqueous alcoholic alkali hydrolyzes the smaller molecular weight alkaloids to lysergic acid and 2-aminopropanol-1, the latter possibly by reduction from alanine. Ergonovine, the most active alkaloid is, therefore, the hydroxyisopropylamide of lysergic acid.[102]

Though not yet synthesized, *lysergic acid* is known to be probably an indoloquinoline. It contains an N-methyl and a carboxyl group; resists acetylation, as does also its dihydro derivative (from reduction by catalytic hydrogen or sodium and amyl alcohol); forms stable salts with one equivalent of acid only; loses carbon dioxide and methyl amine at 210 to 230°; and produces the same color with dimethylaminobenzaldehyde and hydrochloric acid that indole compounds do. Dihydrolysergic acid, when fused with potassium hydroxide in an atmosphere of hydrogen, gives methyl amine almost quantitatively, 1-methyl-5-aminonaphthalein, and an alkylindole, which, because it gives a color test with dimethylaminobenzaldehyde, must have an alpha or beta position unoccupied. Ultraviolet-light absorptions of dihydrolysergic acid and α,β-dimethylindole are practically identical. Nitric acid oxidizes lysergic acid to a tribasic product with an N-methyl group, $C_{14}H_9NO_8$, and this acid, by distillation over soda lime, gives quinoline. These results[103] indicate that lysergic acid is a tetracyclic system with an indole and quinoline nucleus; and the former suggests an origin from tryptophan. The color test with dimethylaminobenzaldehyde indicates an unoccupied alpha or beta position in indole; hence the arrangement of rings must differ from that in harman. The formula[104] below fulfills these requirements. Two diagrams are shown: one to illustrate the numbering system as in "The Ring Index," the other to illustrate better the indole system.

---

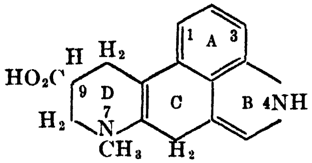
[100] JACOBS and CRAIG, *J. Biol. Chem.*, **145**, 487 (1942).

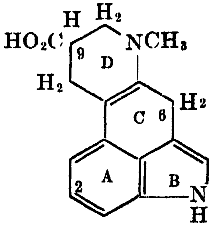
[101] SMITH and TIMMIS, *J. Chem. Soc.*, 763, 1543 (1932); 674 (1934).

[102] JACOBS and CRAIG, *Science*, **82**, 16 (1935).

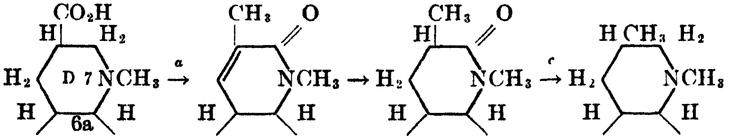
[103] JACOBS and CRAIG, *J. Biol. Chem.*, **111**, 455 (1935); **113**, 767 (1936); **115**, 227 (1936).

[104] GOULD, JACOBS, and CRAIG, *ibid.*, **145**, 487 (1942).



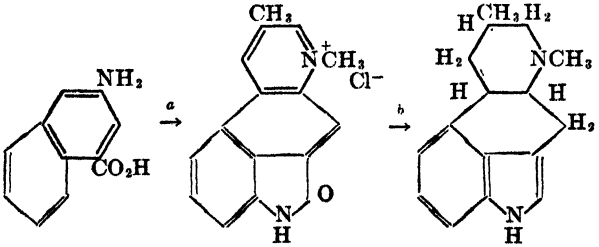


Vacuum sublimation of dihydrolysergic acid (from *dl*-lysergic acid by sodium-butyl alcohol reduction) at 350° gives an unsaturated lactam, $C_{16}H_{16}N_2O$, which is converted by catalytic hydrogenation to a saturated lactam. Sodium-butyl alcohol reduction reduces this lactam to a hydroxy product that loses water readily. A second catalytic hydrogenation then gives dimethylergoline.[105] These changes, which occur in ring D, are shown below.



[a] Heat at 350°. [b] H_2 + Pt. [c] Na + BuOH, H_2 + Pt.

Synthesis[106] of dimethylergoline is accomplished from 3-amino-1-naphthoic acid (from nitration of 1,8-naphthalic acid and subsequent steps) according to the plan below.



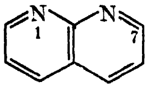
[a] The changes represented here are threefold: one a Skraup synthesis with the α,γ-dimethyl ether of β-methylglycerol to form the quinoline system; the second a nitration, reduction, and lactomization to form the indole system; and the third, a treatment with methyl iodide followed by silver chloride in order to form the methochloride. [b] Reduction by H_2 over Pt in order to form the tetrahydro derivative, further reduction by Na and BuOH.

---

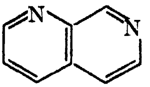
[105] Gould, Craig, and Jacobs, *ibid.*, **145**, 487 (1942).

[106] Jacobs and Gould, *ibid.*, **130**, 399 (1939).

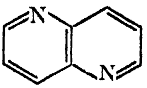
Naphthyridines.—Four examples of naphthyridine compounds are listed below.



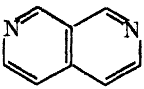
1,8-



1,7-

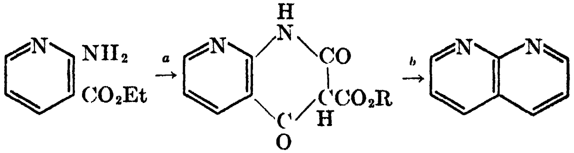


1,5-



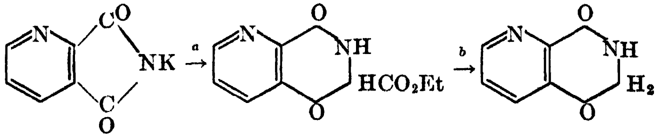
2,7-(copyrine)

Syntheses of compounds that have such frameworks are accomplished by standard methods. A 1,8-product, for instance, is obtained[107] from 2-aminonicotinic acid by the following steps:



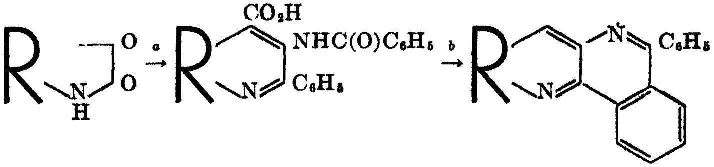
[a] $H_2C(CO_2R)_2$ + NaOR. [b] Saponification and decarboxylation followed by treatment with phosphorus oxychloride and then with hydrogen over palladium.

A derivative of the 1,7- or 2,7-naphthyridine can be obtained[108] from the potassium imide of quinolinic acid (illustrated below) or cinchomeric acid, respectively. The diketo products, incidentally, have the —C(O)-CH_2—NH— system characteristic of indoxyl and, hence, undergo oxidation by hydrogen peroxide or potassium persulfate to a dimer.



[a] $ClCH_2CO_2CH_3$, $NaOCH_3$. [b] HI.

A dibenz-1,5-naphthyridine[109] is synthesized by an adaptation of Pictet and Hubert's preparation of phenanthridines. The compound has some interest because of its similarity to phenanthridine products, which have some trypanocidal activity.



[a] A Pfitzinger reaction with the aminoacetophenone derivative, $C_6H_5C(O)CH_2NHC(O)C_6H_5$. [b] Hot sirupy H_3PO_4 eliminates the carboxyl group, benzoyl chloride and pyridine replace the benzoyl group removed during decarboxylation. The system is now somewhat like a β-phenylethylamine with an N-benzoyl group. Treatment with P_2O_5 at 270 to 280° closes the ring.

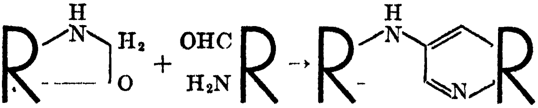
---

[107] KOLLER, *Ber.*, **60**, 407, 1572 (1927).

[108] FELS, *ibid.*, **37**, 2129 (1904); GABRIEL and COLMAN, *ibid.*, **35**, 1358 (1902).

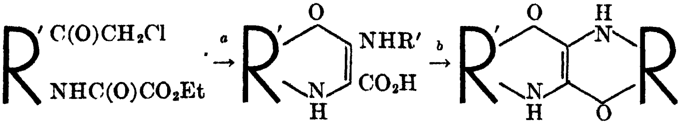
[109] PETROW, STACK, and WRAGG, *J. Chem. Soc.*, 316 (1943).

Quindolines.—*o*-Nitrobenzaldehyde condenses readily with indoxyl. Reduction of the nitro group permits ring closure to a quindoline. *o*-Aminobenzaldehyde, similarly, forms the quindoline (m.p. 248°).[110]



Such condensations of *o*-aminobenzaldehyde with compounds having an active methylene and carbonyl group are common. Hydindone, coumaranone, and thionaphthenone act as does indoxyl.

Epindolines.—The name epindoline[111] is derived from "epi" and "indoline" and is intended to indicate an analogy with quindoline. The dihydroxy derivative, in the isomeric form (epindolidione), is isomeric with indigo and may well be a congener of that compound in some preparations. Preparation of dimethylepindolidione is outlined below. The yellow fibrous crystalline product is insoluble in most organic solvents and is sparingly soluble in boiling quinoline. The compound is also a dibenz-1,5-naphthyridine derivative.

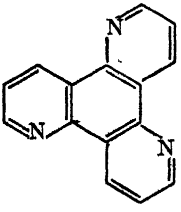


Large $R' = CH_3C_6H_3$. Small $R' = CH_3C_6H_4$. In each case, the methyl group is para to the amino group.

The starting material in this reaction is obtained by the reaction $ClCH_2C(O)C_6H_3(CH_3)NH_2 + EtO_2CC(O)Cl \rightarrow ClCH_2C(O)C_6H_3(CH_3)NHC(O)CO_2Et$.

[a] NaI in acetone, *p*-toluidine, boiling aqueous NaOH. [b] $CH_3OH + H_2SO_4$, $CH_3C(O)Cl$, $SOCl_2$, $AlCl_3$.

Phenotripyridine, pyrido[2,3-*f*]*m*-phenanthridine, known commonly as phenotripyridine, is the analogue of triphenylene.[112] It is prepared in good yield from a mixture of trinitrobenzene, triaminobenzene, glycerol, and sulfuric acid. It melts at 236°, boils above 360°, dissolves in benzene and in chloroform, and crystallizes from alcohol. The solutions have a blue fluorescence.



---

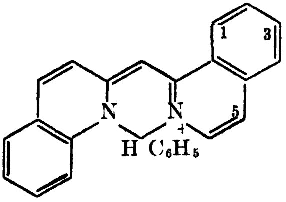
[110] Nölting and Steuer, *Ber.*, **43**, 3512 (1910); Störner and Barthelmes, *ibid.*, **48**, 62 (1915).

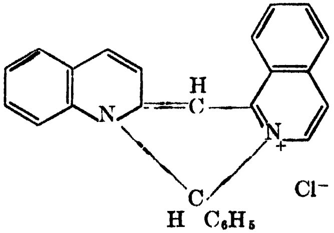
[111] Ainley and Robinson, *J. Chem. Soc.*, 1508 (1934).

[112] Pictet and Barbier, *Bull. soc. chim.* [3], **13**, 28 (1895).

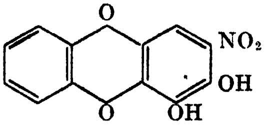
Azanthraquinones.—These anthraquinone-like compounds are used as dye intermediates. The azanthracene[113] is prepared from a β-aminonaphthalene which has the alpha position blocked by a chloro, alkyl, or phenyl group, so that the Skraup synthesis is forced to give a linear rather than the usual angular product. Oxidation of the azanthracene gives the azanthraquinone.

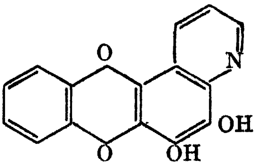
Quinoline Red.—The structure of this compound is represented below by two formulas:[114] the first to accord with the numbering plan, and the second to show the relationship to the cyanine dyes, which it resembles sufficiently to be used in photography. The compound is prepared[115] by heating equimolecular quantities of isoquinoline, quinaldine, and benzotrichloride with zinc chloride at 120°. Oxidation converts the compound to the corresponding diquinolyl ketone.[116]





Alizarin Blue.—This compound has historical value, because a consideration of its formation[117] from alizarin orange led Skraup to try the reaction with simpler compounds and to discover the reaction that bears his name. The yield of alizarin blue is, of course, better from β-aminoalizarin, glycerol. arsenic acid, and sulfuric acid.


Alizarin orange


Alizarin blue

Flavanthrone.—Alkali fusion at 330 to 350°, or treatment with antimony pentachloride in nitrobenzene, converts β-aminoanthraquinone to flavanthrone.[118] The compound crystallizes as yellow-brown needles from boiling quinoline. It forms a soluble blue vat dye with alkaline

---

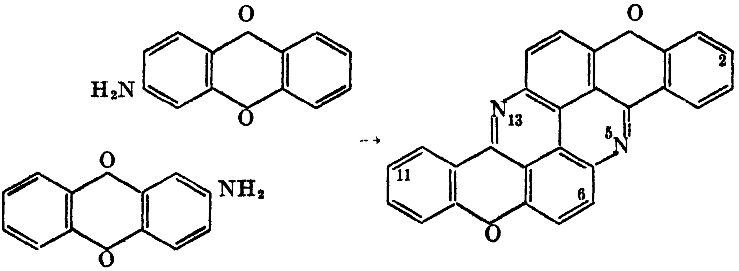
[113] Köberle and Ploetz, U.S. patent 2,003,596; *C.A.*, **29**, 4777 (1935); U.S. patent 2,133,100; *C.A.*, **33**, 875 (1939).

[114] Krantz, *Chem. Weekblad*, **11**, 364 (1914).

[115] Hofmann, *Ber.*, **20**, 4 (1887).

[116] Vongerichten and Hofmann, *ibid.*, **45**, 3446 (1912).

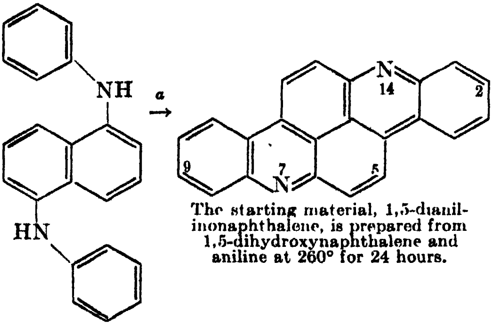
[117] Knueppel, *Ber.*, **29**, 703 (1896).



hydrosulfite which colors cotton a deep blue. The dye is very fast except to light.

The above condensation is general. If the two amino are replaced by methyl groups, and nitric acid or concentrated sulfuric, and potassium nitrate is used as the agent, the corresponding nitrogen-free compound, known as pyranthone, is produced.[119]

Dibenzodiazapyrene.—This compound is prepared by a typical condensation that can be used for preparing phenanthrene and phenanthridine compounds. The chrome-yellow product melts at 362°.[120]



The starting material, 1,5-dianilinonaphthalene, is prepared from 1,5-dihydroxynaphthalene and aniline at 260° for 24 hours.

[a] $AlCl_3$.

Emetine.—Emetine is the principal constituent of ipecac, obtained from the dried rhizome and roots of *Cephaëlis ipecacuanha*, a plant that is native in Brazil and Bolivia and is cultivated in India. It is used as an emetic and an amoebocide. For nearly three centuries, the ipecacuanha root has been a specific cure for dysentery.

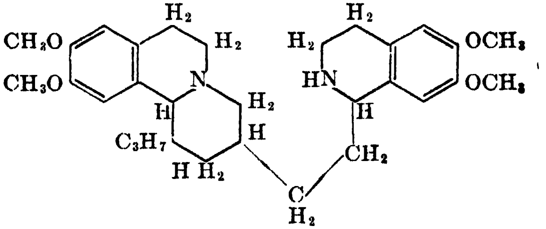
---

[118] Scholl, *ibid.*, **40**, 1691 (1907); Scholl and Dischendorfer, *ibid.*, **51**, 452 (1918).

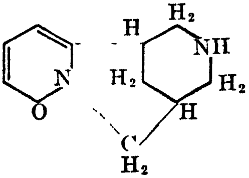
[119] Scholl, *ibid.*, **43**, 346 (1910).

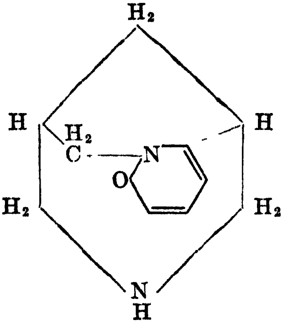
[120] Clemo and Dawson, *J. Chem. Soc.*, 1114 (1939).

The structure is known only by examination of the degradation products. Isoquinoline nuclei are present, but the arrangement of the remainder of the molecule does not appear to resemble too closely the familiar forms of the large group of isoquinoline alkaloids. The formula below accounts for most of the properties so far noted.[121]



Cytisine and Related Compounds.—Cytisine, $C_{11}H_{14}N_2O_2$, occurs in the seeds of *Cytisus laburnum* and a number of other Leguminosae. It acts as a purgative, emetic, and diuretic. The formula appears to be that of a pyridone and piperidine joined by a meta bridge in the latter.[122] It resembles some of the piperidine compounds discussed in Chap. IX but with substituents in the 3,5-positions. The formula is written in two ways below in order to emphasize these features. Nitration and



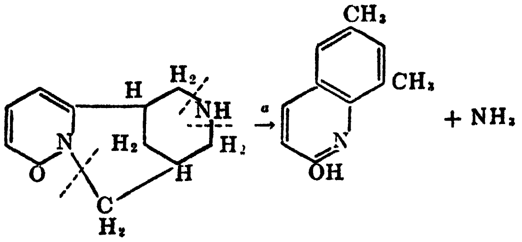


bromination give mono nitro and bromo derivatives, respectively. Mono acyl and nitroso derivatives exist. One of the nitrogen atoms is a weak base, since the common salts are monoacidic (although a dihydrochloride has been obtained). Ring scission, under the influence of hydriodic acid and red phosphorus, eliminates one nitrogen and breaks a bond to the other. The fragments recombine, as a 2-hydroxy-6,8-dimethylquinoline. Barium permanganate and N-methylcytisine gives

---

[121] Brindley and Pyman, *ibid.*, 1067 (1927); Staub, *Helv. Chim. Acta*, **10**, 826 (1927); Späth and Leithe, *Ber.*, **60**, 688 (1927).

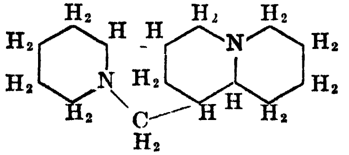
[122] Ing, *J. Chem. Soc.*, 2778 (1932); Späth and Galinovsky, *Ber.*, **66**, 1338 (1933).



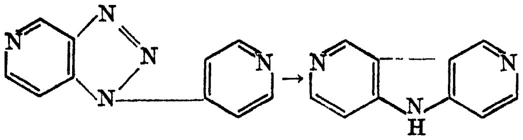
[a] HI + P.

two isomeric lactams, which, in turn, undergo alkaline hydrolysis to amino acids. Formation of two, rather than one, lactam indicates that a methylene group is on either side of the nitrogen atom of the piperidine ring.

The *lupine alkaloids* lupinane and sparteine probably have a framework similar to that of cytisine. A suggested[123] formula for sparteine is shown below.



Diazacarbazole.—This carbazole-like product is obtained by reactions typical of the formation of carbazoles. The compound[124] melts at 300°. It cannot be nitrated, brominated, acetylated, nitrosated, or aminated under the usual conditions. Methyl sulfate forms the N-methyl derivative. It gives no characteristic color reaction with concentrated sulfuric acid, pine splinter and hydrochloric acid, isatin, or benzaldehyde.



Problems

1. Write formulas for the following compounds:[1] (Note: In difficult cases, write the formulas for the parts named on each side of the bracket, number and letter each section independently, then combine the two parts according to the specifications within the brackets.) Benzo[*a*]phenanthridine, dibenz[*f,h*]isoquinoline, naphtho[2,-1-*f*]quinoline, naphtho[2,3-*g*]isoquinoline, quino[8,7-*h*]quinoline, quino[4,3-*b*]quinoline, pyrido[2,3-*f*]1,7-phenanthroline, pyrido[2,3,4,5-*l,m,n*]phenanthridine, 9,18-dioxadibenzo[*a-l*]pentacene.

---

[123] Clemo and Raper, *J. Chem. Soc.*, 644 (1933).

[124] Koenigs and Leopold, *Ber.*, **74**, 215 (1941).

2. *p*-Aminoacetanilide is heated with *o*-bromobenzoic acid, potassium carbonate, and copper at 155° for 4 hr. in amyl alcohol, and the product is treated with 96 per cent sulfuric acid at 100° for 3 hr. The same final product is obtained from potassium anthranilate and *p*-bromonitrobenzene in the presence of copper after 3 hr. in boiling nitrobenzene followed by treatment first with ferrous sulfate and sulfuric acid and then with 96 per cent sulfuric acid at 100°.[13] What product is formed?

3. The anilide of phenylacetic acid, when treated with phosphorus pentachloride, yields a product that has the composition $C_{28}H_{22}N_2$. Chloroacetanilide, by a similar treatment, yields a compound that has the composition $C_{16}H_{12}N_2Cl_2$. The dianilide of pimelic acid, $C_6H_5NHC(O)(CH_2)_5C(O)NHC_6H_5$, with phosphorus pentachloride forms a product that has the composition $C_{19}H_{18}N_2$. Treatment of this last compound with concentrated hydrochloric acid gives 1 molecule of aniline and a product of the composition $C_{13}H_{13}NO$. Reduction of the C_{19} compound with sodium and alcohol gives aniline and $C_{13}H_{17}N$. The type of condensation with phosphorus pentachloride is the same in each case. Suggest plausible structures[125] for the products formed. This condensation is unlike any described in the text but the products can be correctly predicted from consideration of the fragments eliminated in the condensation, the likely positions from which the elimination can occur, and the reasonable assumption that a heterocyclic ring is formed.

4. Suggest the probable product of the compound that has the empirical formula indicated and is made from the reagents listed. (*a*) $C_{13}H_8N_2O_2$ from 2-aminobenzaldehyde with *p*-nitrobromobenzene followed by treatment with concentrated sulfuric acid.[3] (*b*) $C_{19}H_{12}N_2O_2$ from 5- or 6-aminoquinoline (how prepared?) with benzaldehyde and pyruvic acid in absolute alcohol.[126] (*c*) $C_{15}H_{10}N_2$ from *o*-nitrobenzaldehyde with indoxylic acid followed by treatment with zinc dust in acetic acid.[110] (*d*) $C_{14}H_{13}NO_2$ from isatin with cyclohexanone in the presence of 30 per cent potassium hydroxide.[127]

5. What is the product from each of the following reactions? (*a*) *p*-Tolylanthranil, dissolved in strong sulfuric acid at −10° and treated with powdered sodium nitrite.[16] (*b*) Diphenylamine heated with succinic acid and anhydrous zinc chloride.[128] (*c*) 4,4′-Diaminodiphenylmethane sulfate, treated with nitric acid, the dinitro product heated with stannous chloride under pressure, and the product of this reaction oxidized.[51] (*d*) Benzoyldiphenylamine treated with anhydrous zinc chloride at 210 to 280°.[5] (*e*) A mixture of valeric acid and diphenylamine heated with zinc chloride at 200 to 220° for 24 hr.[5] (*f*) *o*-Chlorobenzaldehyde, 2,4-dinitroaniline, and sodium carbonate heated with copper in nitrobenzene, and the product then treated with concentrated sulfuric acid.[13] (*g*) One mole of *m*-phenylenediamine, four moles of glycerol, one mole of oxalic dihydrate; and one and a third mole of zinc chloride heated[17] for 45 minutes at 155°. (*h*) β-Naphthylamine, refluxed with benzylidene-β-naphthyl amine in alcohol for 15 hr.[129] (*i*) 2,2′-Dihydroxy-1,1′-dinaphthylmethane, heated under pressure and at elevated temperatures with an aqueous solution of ammonia.[130] (*j*) 3-β-Aminoethylindole heated for 1 min. with formaldehyde in the presence of sulfuric acid.[131]

---

[125] v. Braun, Heymons, and Menz, *ibid.*, **64**, 227 (1931).

[126] Willgerodt, v. Neander, and Jablonski, *ibid.*, **33**, 2918, 2928 (1900).

[127] Borsche, *Ann.*, **377**, 70 (1910); *Ber.*, **41**, 2203 (1908).

[128] Schenk, *ibid.*, **39**, 2425 (1906).

[129] Haase, *ibid.*, **36**, 591 (1903).

[130] Lehmann, U.S. patent 2,242,585; *C.A.* **35**, 5648 (1941).

[131] Späth and Lederer, *Ber.*, **63**, 2102 (1900).

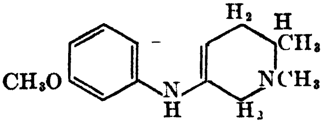
6. Suggest a reaction or a sequence of reactions for preparing each of the following compounds: (*a*) 9-Phenyl-2,7-dimethylacridine.[14] (*b*) 3-Nitro-9-methylphenanthridine.[132] (*c*) *m*-Phenanthroline-6-carboxylic acid.[133] (*d*) 6-Bromobenzene[*h*]quinoline.[134]

7. What is the formula of the $C_{19}H_{11}NO$ compound produced from carbazole by the following succession of reagents: (*a*) potassium hydroxide in acetone solution with *o*-nitrobenzoyl chloride, (*b*) zinc dust and acetic acid, (*c*) sodium nitrite in sulfuric acid, and (*d*) heat? What name or names might be given the compound? What is the numbering according to "The Ring Index"?[135]

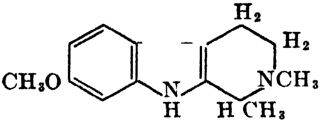
8. When dry calcium anthranilate is heated at 340°, a $C_{26}H_{22}ON_4$ product is obtained. Distillation with zinc dust gives acridine. A saturated hydrochloric acid solution at 170° gives acridone. Suggest a mechanism that accounts for these products.[136]

9. 2,7-Diamino-10-methyl acridinium chloride is less effective against streptococcus than the isomeric acriflavine. Suggest a method for preparing this compound from acridine.[137]

10. Tetrahydroharmine and potassium permanganate yield a $C_{18}H_4N_2O_2$ compound that is neutral and forms no chloro derivative with phosphorus pentachloride or phosphorus oxychloride. What bearing do these facts have on a decision between the two possible formulas written below for tetrahydroharmine?[91]



or



11. The product of reaction of *o*-nitrobenzyl chloride with benzene and aluminum chloride is reduced by tin and hydrochloric acid, and then treated first with nitrous acid, and then with arsenious oxide, alkali, and ammoniacal copper sulfate to form $C_{13}H_{13}O_3As$. When this last compound is dissolved in concentrated sulfuric acid and heated for a few minutes on a water bath, and the solution poured in water, crystals are obtained which have the composition $C_{13}H_{11}O_2As$. Name the final product.[138]

12. What is the probable structure of the $C_{18}H_{10}N_2$ product formed when 9-phenyl-9-fluorylamine, $C_{19}H_{15}N$, is treated with potassium amide and potassium nitrate in liquid ammonia?[139]

13. When 2-aminopyridine is refluxed in a dimethylaniline solution of picryl chloride for 2½ hr., nitrogen oxides are evolved, and a product that has the composition $C_{11}H_6N_4O_4$ is formed. Explain the reaction. By a similar treatment, 6-aminophenanthridine is converted to $C_{19}H_{10}N_4O_4$. What product is formed?[140]

14. When the product of the condensation of *m*-aminoacetanlide with ethyl acetoacetate is heated in paraffin at 260°, a small amount of a compound of composition $C_{12}H_{12}N_2O_2$ is obtained. This product is boiled with 33 per cent hydrochloric acid and then treated with glycerol, arsenic acid, and concentrated sulfuric acid. What is the structure[141] of the $C_{13}H_{10}N_2O$ product?

---

[132] Morgan and Walls, *J. Chem. Soc.*, 2225 (1932).

[133] Skraup and Fischer, *Monatsh.*, **5**, 523 (1884).

[134] Utermohlen Jr. and Hamilton, *J. Am. Chem. Soc.*, **63**, 156 (1941).

[135] Plant and Tomlinson, *J. Chem. Soc.*, 2188 (1932).

[136] Koller and Krakauer, *Monatsh.*, **50**, 51 (1928).

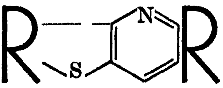
[137] Lehmstedt and Hundertmark, *Ber.*, **64**, 2386 (1931).

[138] Gump and Stoltzenberg, *J. Am. Chem. Soc.*, **53**, 1428 (1931).

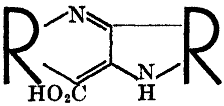
[139] White and Bergstrom, *J. Org. Chem.*, **7**, 497 (1942).

[140] Morgan and Stewart, *J. Chem. Soc.*, 1292 (1938).

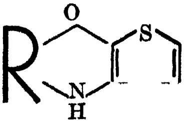
15. Devise methods for synthesizing the following compounds from accessible or easily prepared reagents.



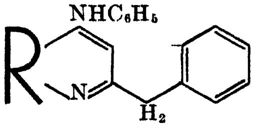
110



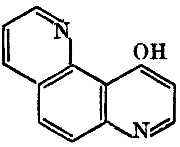
142



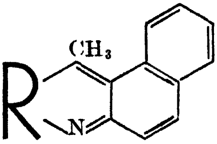
143



125



144

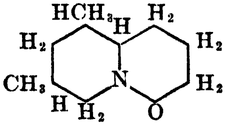


145

Apply the same method as was used for the last compound, or a closely related method, to the preparation of 1,2,5,6-dibenz-9-fluorene.[145]

16. Addition of lime to a well-stirred mixture of cyclohexanone, formaldehyde, and water yields a product that is coverted by aniline in the presence of stannic chloride to a compound that has the composition $C_{13}H_{13}N$. When this last compound is heated with selenium at 270° to 320°, the product is $C_{13}H_9N$.[146] What changes are involved?

17. Suggest a method for synthesis of the degradation product, shown below, of cytisine.[147]



---

[141] Kermack and Webster, *ibid.*, 213 (1942).

[142] Fishter and Rohner, *Ber.*, **43**, 3489 (1910).

[143] Steinkopf and Günther, *Ann.*, **522**, 28 (1936).

[144] Kermack and Tebrich, *J. Chem. Soc.*, 375 (1945).

[145] Berliner, *J. Am. Chem. Soc.*, **64**, 2894 (1942).

[146] Kenner, Ritchie, and Statham, *J. Chem. Soc.*, 1169 (1937).

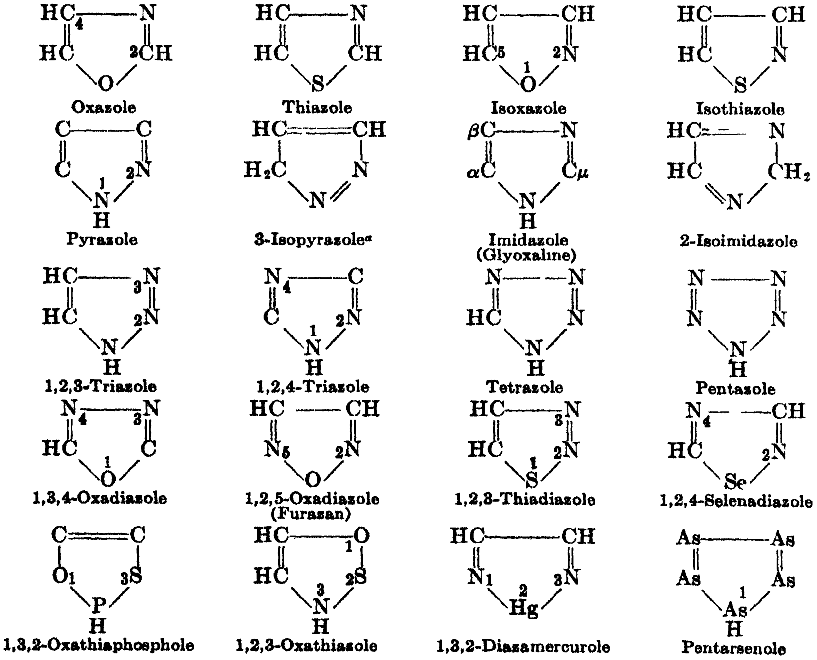
[147] Späth and Galinovsky, *Ber.*, **71**, 721 (1938).

CHAPTER XIII

AZOLES, AZOLONES, AND RELATED SYSTEMS

PART I

The ending *-azole* designates a five-membered ring system with two or more heteroatoms, one of which is nitrogen. The compounds may be regarded as being formed by replacement of a carbon by a nitrogen atom in a ring that already contains one or more hetero atoms; or, as originally defined,[1] by replacement of a double methine group by a hetero atom (O, S, or NH) in a compound of the pyridine type. The azoles are grouped together in this text because many of the methods of preparation are common to large numbers of compounds, irrespective of the hetero atoms present; and because the reactions that they undergo are similar,



[a] Known only in its derivatives.

FIG. 1.—Naming and numbering of typical monocyclic azole and related systems.

---

[1] HANTZSCH, *Ann.*, **249**, 1 (1888).

The name reveals the type. Oxazoles, thiazoles, or selenazoles contain an oxygen, sulfur, or selenium atom, separated from nitrogen by a carbon atom (see Fig. 1). *Iso-*, prefixed to these names, designates the corresponding isomeric compound with the hetero atoms adjacent to each other. Imidazoles contain an imide system, separated from nitrogen by a carbon atom. They are cyclic amidines. Pyrazoles, theoretically derived from pyrroles, have the two nitrogen atoms adjacent to each other. Triazoles and tetrazoles have three and four nitrogen atoms, respectively.

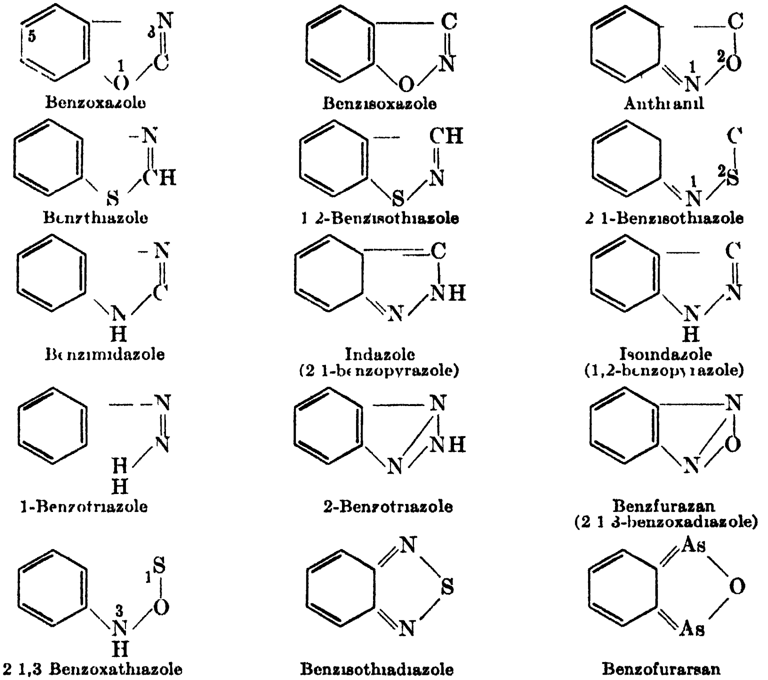

Benzoxazole
Benzisoxazole
Anthranil
Benzthiazole
1,2-Benzisothiazole
2,1-Benzisothiazole
Benzimidazole
Indazole
(2,1-benzopyrazole)
Isoindazole
(1,2-benzopyrazole)
1-Benzotriazole
2-Benzotriazole
Benzfurazan
(2,1,3-benzoxadiazole)
2,1,3 Benzoxathiazole
Benzisothiadiazole
Benzofurarsan

FIG. 2.—Naming and numbering of some benzazole compounds. Some of the compounds are represented as having a 1,3-bridge. The problem of an alternative structure as shown for indazole will be discussed later in this chapter.

Glyoxaline is an empirical name, used sometimes for imidazoles, because the parent member of the series was first derived from glyoxal and ammonia. The term furazan, another empirical name commonly used in place of 1,2,5-oxadiazoles, is derived from the relationship to furan.

Azolines are partly reduced and azolidines are completely reduced azoles. If oxygen is present as a substituent and has reactions which show that it exists in the keto rather than the enol form, the ending *-lone* is attached. Examples are oxazolone, thiazolone, imidazolone.

The ending *-ole* is used for other five-membered heterocyclic ring systems without nitrogen. Examples are 1,2,3-trithiole, $C_2H_2S_3$, and 1,3,2-dithiastibole, $C_2H_3S_2Sb$. Occasionally a compound is not an azole in spite of the ending. Carbazole is a long-established exception to the general rule. Prontosil was at one time incorrectly called rubiazole.

The numbering of monocyclic azole systems (see Fig. 1) begins with the hetero atom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. For example, in an oxazole, the numbering begins with the oxygen atom and progresses by the shortest path to the nitrogen atom; in a thiazole it begins with the sulfur atom; in an oxathiazole it starts with oxygen, progresses to sulfur and thence to nitrogen. Imidazoles have two nitrogen atoms, either of which may be the starting point. For that reason, the alternative numbering is usually designated in parentheses, as in 4(5) bromoimidazole.

If the system is bicyclic, as in the case of benzoxazole, the numbering begins with an atom nearest the benz ring, a hetero-atom, if possible. It follows, therefore, that the order of numbering, as prescribed for monocyclic systems, is sometimes modified. Anthranil and benzofuran (Fig. 2) are examples.

METHODS FOR THE PREPARATION OF AZOLES

Since many preparative methods are common to a number of different types, and since the process used for one frequently suggests a way for the preparation of other types, the various methods are grouped, in order to emphasize the similarity.

From 1,4-dienol Compounds.—Compounds that have (or by enolization are capable of having) two hydroxy groups, or an amino and a hydroxy group in the 1,4-positions, readily undergo ring closure when an oxygen, sulfur, or nitrogen atom is available to fill the gap. The process is essentially that used for making a furan, thiophene, or pyrrole. Figure 3 shows numerous combinations, arranged in order for the production of compounds with three carbon atoms joined together in the ring (example 1), two carbon atoms so linked (examples 2, 3, and 4), and finally one carbon atom linked directly to no other carbon but to nitrogen (examples 5 and 6). The first example shows the formation of an isoxazole from the monoxime of a 1,3-diketone system, a process that occurs with extreme ease. The second shows the preparation of an oxazole or thiazole by ring closure of the acyl or like derivative of an α-aminoketone, aldehyde, or acetal. The third shows ring closure of the dioxime of a 1,2-dialdehyde or diketone. The fourth is a combination of an enolizable ketone with a hydroxy azo reagent. In the particular example shown, the α-amino compound, derived by the action of ammonia on ethyl acetoacetate, is treated with nitrous acid to give the intermediate necessary for ring closure. The fifth example shows the way in which a diacethydrazide or other similar hydrazine derivative can be converted to a heterocyclic azole compound. So impressed was Stollé[2] by the similarity between this reaction and the formation of the mono hetero five-membered ring compounds that he called the products furodiazoles, thiadiazoles, and pyrrodiazoles, depending on the hetero atom introduced. In the last example, a hydroxy-amino system, which is obtained

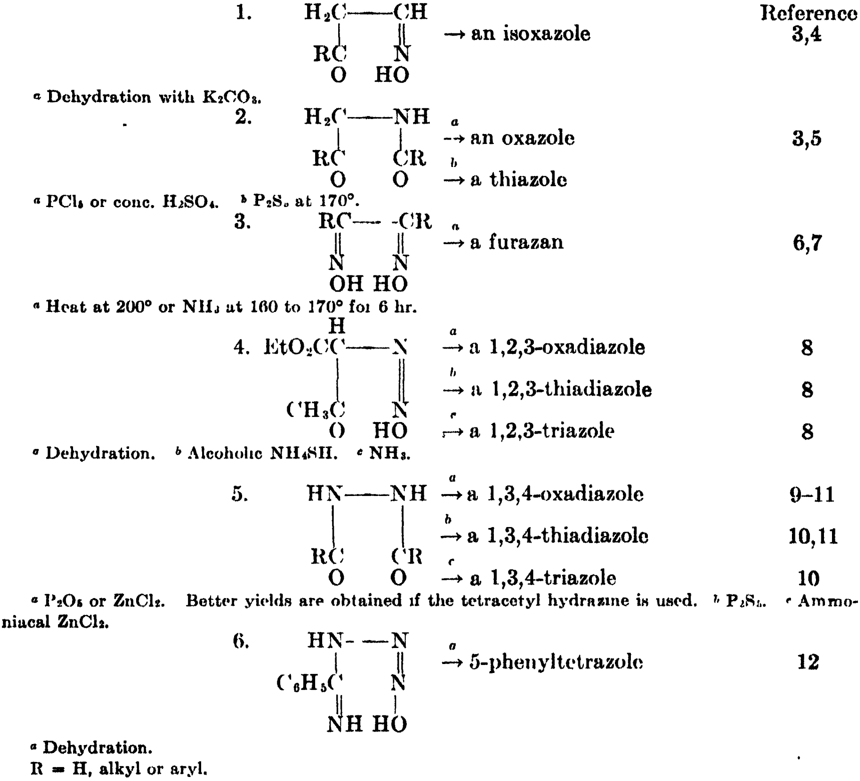

Reference
1. → an isoxazole 3,4
a Dehydration with K₂CO₃.
2. a → an oxazole 3,5
b → a thiazole
a PCl₅ or conc. H₂SO₄. b P₂S₅ at 170°.
3. a → a furazan 6,7
a Heat at 200° or NH₃ at 160 to 170° for 6 hr.
4. a → a 1,2,3-oxadiazole 8
b → a 1,2,3-thiadiazole 8
c → a 1,2,3-triazole 8
a Dehydration. b Alcoholic NH₄SH. c NH₃.
5. a → a 1,3,4-oxadiazole 9–11
b → a 1,3,4-thiadiazole 10,11
c → a 1,3,4-triazole 10
a P₂O₅ or ZnCl₂. Better yields are obtained if the tetracetyl hydrazine is used. b P₂S₅. c Ammoniacal ZnCl₂.
6. a → 5-phenyltetrazole 12
a Dehydration.
R = H, alkyl or aryl.

FIG. 3.—Methods for preparing azoles by ring closure of 1,4-dienol or related systems.

[2] STOLLÉ, *Ber.*, **32**, 797 (1899).

References to Fig. 3

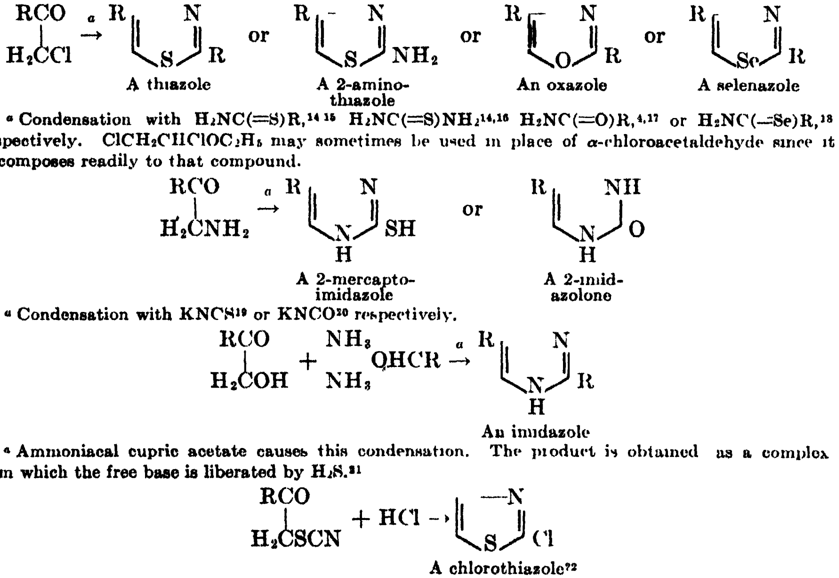
[3] GABRIEL, *Ber.*, **43**, 134, 1283 (1910).
[4] ROBINSON, *J. Chem. Soc.*, **95**, 2167 (1907).
[5] BACHSTEZ, *Ber.*, **47**, 3163 (1914).
[6] WOLFF, *ibid.*, **28**, 69 (1895); *Ann.*, **260**, 79 (1890).
[7] v. AUWERS and MEYER, *Ber.*, **21**, 784 (1888).
[8] WOLFF, *Ann.*, **325**, 129 (1902).
[9] GÜNTHER, *ibid.*, **252**, 44 (1889).
[10] STOLLÉ, *Ber.*, **32**, 797 (1899); *J. prakt. Chem.* [2], **68**, 130 (1903); PELLIZZARI, MASSA, and ALCIATORE, *Atti accad. Lincei* [5], **10**, I, 365, 444 (1901).
[11] DIMROTH and DE MONTMOLLIN, *Ber.*, **43**, 2904 (1910).
[12] PINNER, *Ann.*, **297**, 221 (1897).

from the iminohydrazide of benzoic acid, $C_6H_5C(=NH)NHNH_2$, by treatment with nitrous acid, loses water to give a tetrazole. The iminohydrazide[13] is obtained from the nitrile by a process that parallels the preparation of amidines save for the use of hydrazine in place of ammonia.

$$RCN \xrightarrow{a} RC(=NH)OC_2H_5 \xrightarrow{b} RC(=NH)NHNH_2$$

[a] $C_2H_5OH + HCl$. [b] H_2NNH_2.

From α-Substituted Ketones.—A second general method is to condense an α-substituted ketone or aldehyde with an appropriate reagent



A thiazole — A 2-aminothiazole — An oxazole — A selenazole

[a] Condensation with $H_2NC(=S)R$,[14,15] $H_2NC(=S)NH_2$,[14,16] $H_2NC(=O)R$,[4,17] or $H_2NC(=Se)R$,[18] respectively. $ClCH_2CHClOC_2H_5$ may sometimes be used in place of α-chloroacetaldehyde since it decomposes readily to that compound.

A 2-mercaptoimidazole — A 2-imidazolone

[a] Condensation with KNCS[19] or KNCO[20] respectively.

An imidazole

[a] Ammoniacal cupric acetate causes this condensation. The product is obtained as a complex from which the free base is liberated by H_2S.[21]

A chlorothiazole[22]

R = H, alkyl or aryl group.

FIG. 4.—Preparation of azoles from α-substituted ketones or aldehydes.

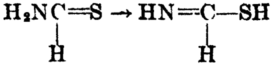
or reagents that will fill in the necessary parts. The most common compounds are α-chloro-, α-amino-, or α-hydroxy-derivatives. The reagents with which they condense are thioamides, thiourea, amides, thiocyanates, cyanates, and like substances. Examples of this type of formation are shown in Fig. 4. In the first group, the chloro- or bromo-ketone con-

[13] PINNER, *Ann.*, 207, 221 (1897).

References to Fig. 4

[14] HANTZSCH, *Ann.*, **250**, 257 (1888).
[15] HUBACHER, *ibid.*, **259**, 228 (1890).
[16] WOHMANN, *ibid.*, **259**, 277 (1890).
[17] LEWY, *Ber.*, **20**, 2576 (1887).
[18] HOFMANN, *Ann.*, **250**, 316 (1888).
[19] WOHL and MARCKWALD, *Ber.*, **22**, 568, 1353 (1889); MARCKWALD, *ibid.*, **25**, 2354 (1892).
[20] OCHIAI and IKUMA, *ibid.*, **69**, 1147 (1936).
[21] WEIDENHAGEN and HERRMANN, *ibid.*, **68**, 1953 (1935).
[22] TCHERNIAC, *J. Chem. Soc.*, **115**, 1071 (1919).

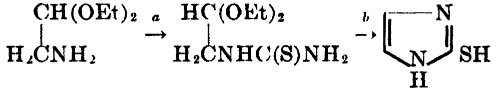
denses with a three-atom system, as in thioamides or thiourea, by elimination of hydrochloric or hydrobromic acid, the hydrogen for which always comes from the bivalent sulfur, oxygen, or selenium atom, by way of a preliminary enolization, as indicated below.



$$H_2N\underset{H}{C}{=}S \rightarrow HN{=}\underset{H}{C}{-}SH$$

Though amides condense as do thioamides in this reaction, urea does not condense as does thiourea but yields an imidazolone rather than an aminooxazole.

The second group shows the reaction of α-amino-ketones, -aldehydes, or -acetals, with a thiocyanate or cyanate to give a 2-mercaptoimidazole or a 2-imidazolone, respectively. Like many other reactions, this one takes place in steps, which, at times, can be isolated, as shown below in the case of a thiourea derivative.[23]



[a] KCNS. [b] 140°.

α-Hydroxy-substituted ketones or aldehydes condense with ammonia and formaldehyde under the mild oxidizing influence of ammoniacal cupric acetate. The reaction proceeds by way of oxidation of the hydroxy ketone to a diketone, which then undergoes a condensation, characteristic of all such diketones[24] (see page 449). Synthesis from the α-hydroxy ketone is frequently simpler than with diketones because the starting material is obtained so readily.

In the last example of Fig. 4, a ketone, with an α-thiocyano substituent, undergoes ring closure by treatment with hydrochloric or hydrobromic acid. If the acid adds across the C≡N group, this process would resemble also the 1,4-dienol system mentioned before. The halogen atom can be removed subsequently by zinc and acetic acid.

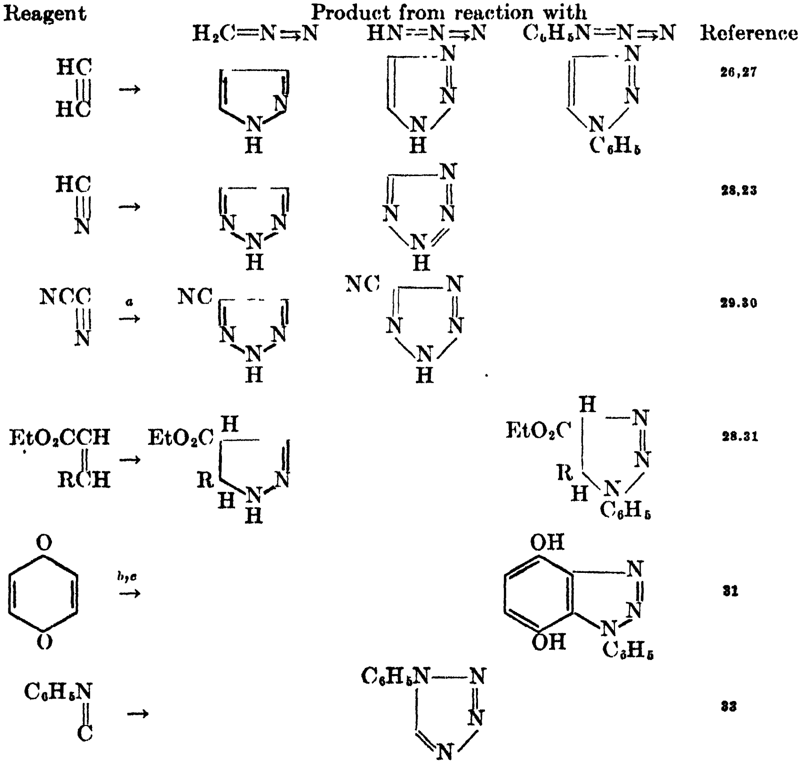
The necessary α-substituted ketones or aldehydes are obtained by conventional methods. For example, α-amino compounds are formed by reduction of isonitroso ketones obtained by the action of nitrous acid on ketones. The oxime is reduced to the α-amino ketone by stannous chloride and hydrochloric acid or by catalytic hydrogen.[20] It is not always necessary to isolate the amino product from this reduction, before addition of the thiocyanate. α-Chloro- or α-bromo ketones are made by halogenation of the ketone. α-Hydroxy ketones are derived by hydrolysis of the brominated ketone. The thiocyanate compound is also obtained from the halogenated ketone by reaction with alkaline thiocyanate.

---

[23] Marckwald, *Ber.*, **25**, 2354 (1892).

[24] Radiziszewski, *ibid.*, **15**, 2706 (1882); **16**, 487 (1883).

Formation of 1,2,4-triazoles[25] from formylhydrazine and formamide (see next page) is essentially the same process as that which uses α-amino



[a] The CN substituent may undergo condensation with a second molecule of reagent to give a bisazole product.

[b] Hydrazoic acid adds to give an azidohydroquinone, $HOC_6H_3(N_3)OH$.

[c] Excess quinone oxidizes the triazole product to a quinone.

FIG. 5.—Addition of diazo compounds and azides to some triple and double bonds.

ketones, save for the fact that the amino group is attached to a nitrogen instead of a carbon atom. So also may the condensation of formylhydrazine with itself to form an aminotriazole[32,33] be classed with this group.

---

[25] PELLIZZARI, *Gazz. chim. ital.*, **24**, II, 223 (1894); **39**, I, 520 (1909).

[26] v. PECHMANN, *Ber.*, **31**, 2950 (1898).

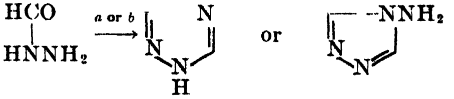
[27] DIMROTH and FESTER, *ibid.*, **43**, 2219 (1910); FORSTER and NEWMAN, *J. Chem. Soc.*, **97**, 2570 (1910).

[28] v. PECHMANN and BURKHARD, **33**, 3590 (1901); v. AUWERS and UNGEMACH, *ibid.*, **66**, 1205 (1933); HURD and LUI, *J. Am. Chem. Soc.*, **57**, 2657 (1935); ADAMSON and KENNER, *J. Chem. Soc.*, 286 (1935).

[29] PERATONER, *Gazz. chim. ital.*, **38**, I, 76 (1908).

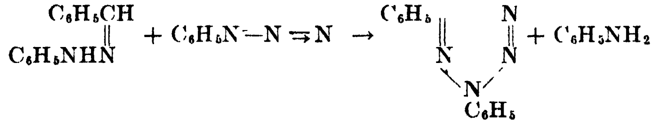
[30] OLIVERIÓ, MANDALA, and PASSALACQUA, *ibid.*, **41**, II, 430 (1911); CURTIUS, DARAPSKY, and MÜLLER, *Ber.*, **48**, 1614 (1915).

[31] WOLFF and GRAU, *Ann.*, **394**, 68 (1912); FIESER and PETERS, *J. Am. Chem. Soc.*, **53**, 4080 (1931); FIESER and HARTWELL, *ibid.*, **57**, 1479 (1935).



[a] Condensation with H_2NCHO. [b] Condensation with $H_2NNHCHO$.

By Addition of Azo and Azide Compounds to Unsaturated Systems.— A third method, applicable to the preparation of azoles with two or more nitrogen atoms, consists of the 1,3-addition[34] which diazo compounds (diazomethane, ethyl diazoacetate) or azides (hydrazoic acid, phenylazide) undergo with triple- or double-bonded systems. Acetylene and its derivatives, hydrogen cyanide and cyanogen, are suitable as triple-bond reagents; olefins in general, but more particularly ethyl crotonate, ethyl maleate, and other unsaturated esters or ketones, serve as double-bond reagents that form dihydro products; and isocyanides act as unsaturated systems that form azoles. Many examples are shown in Fig. 5. Even the double bond in hydrazones and oximes behaves somewhat in the same manner, as illustrated by the preparation of a tetrazole[35] below.



If the addition of diazomethane or hydrazoic acid to the acetylene, olefin, nitrile, isonitrile, oxime, and hydrazone systems sets a pattern for judging the reaction with all double bonds, these two reagents should similarly add to the carbonyl group of aldehydes, ketones, and acid chlorides. If such heterocyclic products do occur, they serve only as unstable intermediates,[34] for the end results of the processes are open-chain compounds. Nevertheless, the reactions can be represented by a plan that parallels exactly the formation of heterocyclic compounds and the products obtained therefrom can be correctly predicted.

Aldehydes,[36] ordinary ketones,[37] cyclic ketones,[38] and acid chlo-

---

[32] Hantzcsh and Silberrad, *Ber.*, **33**, 85 (1900).

[33] Oliveri-Mandala and Algana, *Gazz. chim. ital.*, **40**, II, 441 (1910).

[34] Smith, *Chem. Rev.*, **23**, 193 (1938).

[35] Dimroth and Merzbacher, *Ber.*, **40**, 2402 (1907).

[36] Arndt, *ibid.*, **60**, 1364 (1927); **61**, 1107, 1122 (1928); **66**, 1012 (1933); *Z. angew. Chem.*, **40**, 1099 (1927); **46**, 47 (1933).

[37] Meerwein, Bersin, and Burneleit, *Ber.*, **62**, 999 (1929); Meerwein and Burneleit, *ibid.*, **61**, 1840 (1928).

[38] Mosettig and Burger, *J. Am. Chem. Soc.*, **52**, 3456 (1930).

rides[39] can be pictured;[34] as forming an unstable dihydrooxadiazole with diazomethane. Nitrogen escapes, and a proton, methyl group, alkyl group, or chloro atom, respectively, rearranges (see Fig. 6). The process appears general, though the decomposition sometimes takes another path. If, in the aldehyde reaction, the proton fails to rearrange, the oxygen atom then moves and an aldehyde, RCH_2CHO, or an epoxy, $\overline{RCH—CH_2—O}$, compound forms. If, in the ketone reaction, the methyl group fails to make the expected shift from C_5 to C_4, the epoxy product,

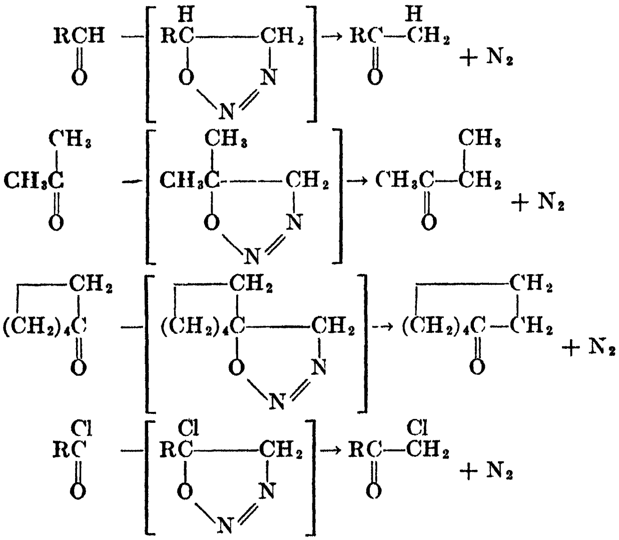


FIG. 6.—Reaction of diazomethane with various compounds that have carbonyl groups.

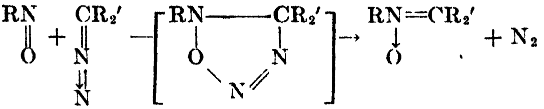
$\overline{(CH_3)_2C—CH_2—O}$ results; and if the intermediate product from the acid chloride loses hydrogen chloride instead of nitrogen, as indeed it does if the acid chloride is added to diazomethane instead of the diazomethane to the acid chloride, the product is a diazoketone. This ketone, in the presence of finely divided metals as catalysts, reacts with water, alcohol, or ammonia to give an acid, ester, or amide, respectively—the well-known Arndt-Eistert reaction.[40]

---

[39] CLIBBENS and NIERENSTEIN, *J. Chem. Soc.*, **107**, 1491 (1915); BRADLEY and ROBINSON, *ibid.*, 1310 (1928); BRADLEY and SCHWARZENBACH, *ibid.*, 2904 (1928); MALKIN and NIERENSTEIN, *ibid.*, **52**, 1507 (1930); BRADLEY and ROBINSON, *ibid.*, **52**, 1558 (1930).

[40] ARNDT and EISTERT, *Ber.*, **68**, 193, 200, 208 (1935); see also WALLIS, *J. Org. Chem.*, **6**, 443 (1941).

Formation of a nitrone[41] from a nitroso compound can be pictured[34] in the same way.



A parallel set of intermediate dihydrooxatriazoles can be assumed to form in the reactions with hydrazoic acid. The processes are illustrated in Fig. 7 with an aldehyde[42] and a ketone from which the products are an amide and an N-substituted amide, respectively. This last reaction is known as the Schmidt reaction.[43]

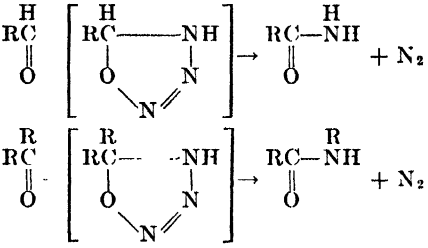


Fig. 7.—Reactions of an hydrazide with aldehydes and ketones.

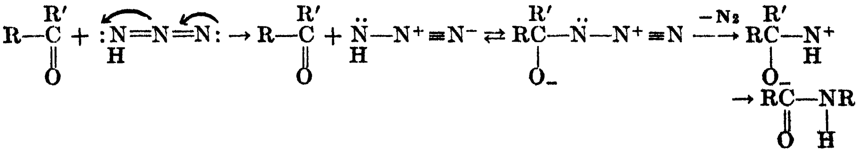
The oxime of a cyclic ketone can be pictured as undergoing a similar ring enlargement when treated with hydrazoic acid. In this case, the product is not a dihydro compound. Hence it does not lose nitrogen

---

[41] v. Pechmann, *Ber.*, **28**, 860 (1895); **30**, 2461, 2872 (1897); **31**, 293, 557 (1898); Staudinger and Miescher, *Helv. Chim. Acta*, **2**, 554, 581 (1919).

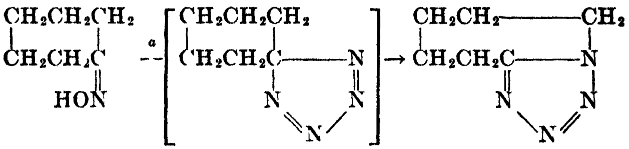
[42] Audrieth, *Chem. Rev.*, **15**, 175 (1934).

[43] A different expression for the mechanism of this reaction has been presented by Briggs and Lyttleton, *J. Chem. Soc.*, 421 (1943), and Hurd, Gilman, "Organic Chemistry," Vol. I, John Wiley & Sons, Inc., New York, 1938. The steps are as shown below.



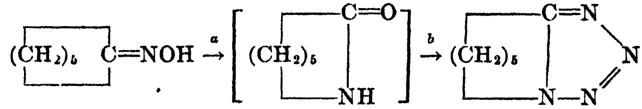
This proposal makes the Schmidt reaction somewhat similar to the decomposition of bromo-amide and of dihydroxamic acid. See Hauser, *J. Am. Chem. Soc.*, **61**, 618 (1939). The assumption of a transitory or incipient dihydroheterocyclic ring compound as an intermediate in this reaction is not intended to controvert any electronic interpretation but is used merely to provide a simple basis for correlation of the chemical behavior of diazomethane, hydrazoic acid, and azides toward all double bonds.

but remains as a stable tetrazole, known in this case as 5-azepotetrazole, pentamethylenetetrazole, or metrazole.



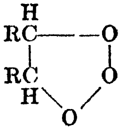
[a] Reaction with NaN_3 in H_2SO_4 at 25 to 35°.

In spite of the similarity of this process to the preceding examples with the carbonyl groups, the course of this reaction may be pictured very well by another excellent mechanism.[44a] Sulfuric acid is known to cause rearrangement of oximes, the product, in the case of the oxime of a cyclic ketone, being a cyclic amide. Reaction with hydrazoic acid would then form the tetrazole, possibly by addition to the C=N bond formed by enolization.



[a] H_2SO_4. [b] HN_3.

Ozone has a structure, $O{=}O\rightleftarrows O$,[44b] similar to that of diazomethane and hydrazoic acid and adds to double and triple carbon-carbon bonds. By analogy, the product from an olefin should be a dihydro-1,2,3-trioxole; this formula was, in fact, proposed by Harries.[45] Though this structure seems very plausible, it is not currently accepted.



The gentlest methods of reducing *ozonides* derived from olefins have so far failed to preserve the carbon-carbon bond. The ozonides derived from acetylene and diphenylacetylene, however, yield glyoxal (in 81 per cent yield)[46] and benzil (in 65 per cent yield); and these ozonides should be more stable because they are not dihydrotrioxoles. Staudinger[47] prefers the formula of a highly unstable "molozonide," which rearranges to the less unstable isozonide. Although the isozonide formula cannot be

---

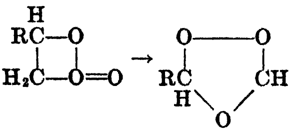
[44a] v. Braun and Heymons, *Ber.*, **63**, 502 (1930).

[44b] Long, *Chem. Rev.*, **27**, 437 (1910).

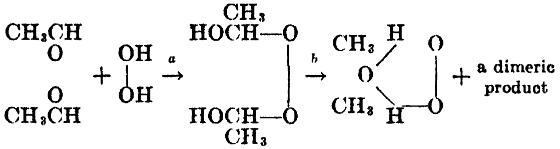
[45] Harries, *Ann.*, **374**, 288 (1910).

[46] Briner and Wunenburger, *Helv. Chim. Acta*, **12**, 786 (1928); Jacobs, *J. Am. Chem. Soc.*, **58**, 2272 (1936); Hurd and Christ, *J. Org. Chem.*, **1**, 141 (1936).

[47] Staudinger, *Ber.*, **58**, 1088 (1925).



regarded as proved unequivocally, it derives support from (*a*) the similarity between ozonides and peroxides in data for molecular refraction, parachor, and ultraviolet absorption; (*b*) the results of hydration of ozonides in which a peroxide is formed; and (*c*) the synthesis[48] (in small yield) from acetaldehyde and a 3 per cent ethereal solution of hydrogen peroxide.



[a] Addition. [b] Dehydration with P_2O_5.

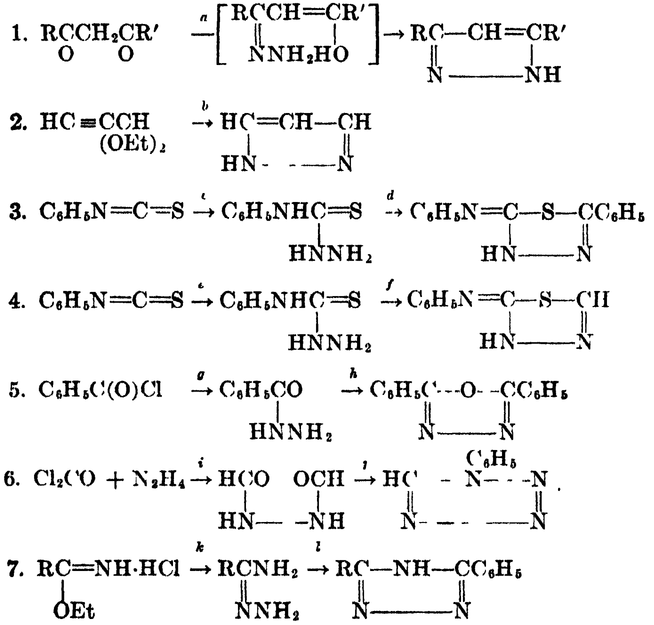
Should ozone add, as does diazomethane, a rearrangement of the dihydro product to an isozonide would not be unexpected. A chain of three atoms of an element in the sixth group of the periodic table should produce a molecule of considerable instability—one prone to decompose or to rearrange to a more stable form. The association of an atom in the fifth with one in the seventh group (nitrogen with chlorine or bromine) creates the instability that promotes such well-known rearrangements as the Beckmann and Hofmann; and these changes occur at the expense of breaking the carbon-carbon bond.

The reactions described in this section may now be summarized from the viewpoint of heterocyclic chemistry. Diazomethane, hydrazoic acid, and ozone form comparatively stable heterocyclic ring compounds by addition to triple carbon-carbon bonds; and diazomethane and hydrazoic acid form stable heterocyclic compounds by addition to such triple bonds as are present in nitriles. These three reagents add also to double bonds, but the stabilities of the dihydro five-membered heterocyclic ring products are limited. The dihydro product from the reaction of diazomethane with olefins will decompose over hot platinum to cyclopropanes; the dihydro product from the reaction of ozone with olefins immediately rearranges to the more stable isozonide. The products of the reaction of diazomethane and hydrazoic acid with other double bonds, such as a carbonyl group, may be regarded as transitory or incipient dihydro heterocyclic five-membered rings that lose nitrogen spontaneously and undergo a simultaneous rearrangement of a group attached to the carbon of the carbonyl group. In some of these reactions, special electronic interpretations have been offered which are very suitable for interpreting the action.

---

[48] RIECHE and MEISTER, *ibid.*, 65, 1274 (1932).

Preparation from Hydrazines.—A fourth method for the preparation of azoles utilizes the capacity of hydrazine to undergo condensation, addition, or substitution at both ends of the molecule. In many instances, the final act of ring closure is achieved through a 1,4-dienol system. Already a few illustrations of this type have been presented in Fig. 3; and a number of other combinations is now illustrated in Fig. 8. The first reaction is the well-known method of forming pyrazoles from the reaction of 1,3-diketones or dialdehydes with hydrazines. The reaction probably proceeds by the intermediate steps shown in brackets, since in most cases there is a difference in the velocity of combination at the two


1. $RCCH_2CR'$ O O
$\xrightarrow{a}$ [RCCH=CR' NNH₂HO] → RC—CH=CR' N—NH
2. HC≡CCH (OEt)₂ $\xrightarrow{b}$ HC=CH—CH HN—N
3. $C_6H_5N=C=S \xrightarrow{c} C_6H_5NHC=S$ HNNH₂ $\xrightarrow{d} C_6H_5N=C—S—CC_6H_5$ HN—N
4. $C_6H_5N=C=S \xrightarrow{e} C_6H_5NHC=S$ HNNH₂ $\xrightarrow{f} C_6H_5N=C—S—CH$ HN—N
5. $C_6H_5C(O)Cl \xrightarrow{g} C_6H_5CO$ HNNH₂ $\xrightarrow{h} C_6H_5C—O—CC_6H_5$ N—N
6. $Cl_2CO + N_2H_4 \xrightarrow{i}$ HCO OCH HN—NH $\xrightarrow{j}$ HC—N(C₆H₅)—N N—N
7. RC=NH·HCl OEt $\xrightarrow{k}$ RCNH₂ NNH₂ $\xrightarrow{l}$ RC—NH—CC₆H₅ N—N

[a] Heat at 40 to 50° effects the condensation.[49] [b] Addition of the hydrazine across the triple bond occurs, followed by elimination of 2 molecules of alcohol.[50] [c] Addition reaction. [d] Reaction with benzaldehyde forms a benzal derivative which then forms the thiadiazole ring under the influence of hot formic acid.[51] [e] Addition reaction. [f] Hot formic acid gives the formyl derivative which then undergoes ring closure.[51] [g] Benzoyl chloride forms the hydrazide. [h] Benzaldehyde yields the benzal derivative of the hydrazide after which potassium ferricyanide induces ring closure.[10] [i] Phosgene forms the diformyl derivative. [j] Benzene diazonium chloride displaces one formyl group and forms the compound $HC(O)NHN{=}N{-}NHC_6H_5$ which undergoes ring closure to give the tetrazol.[11] [k] The imino ether condenses with hydrazine in the presence of KOH.[12] [l] $C_6H_5C(O)Cl$ followed by heat.[12]

FIG. 8.—Use of hydrazine in the preparation of azoles.

---

[49] v. AUWERS and DIETRICH, *J. prakt. Chem.*, **139**, 65 (1934); MUMM and BERGELL, *Ber.*, **45**, 3040 (1912).

[50] CLAISEN, *ibid.*, **36**, 3666 (1903).

[51] PULVERMACHER, *ibid.*, **27**, 613 (1894).

carbonyl groups. The second example is an addition-condensation process between hydrazine and propargyldiethylacetal, which leads to a pyrazole. This type of reaction, when carried out between a vinyl ketone and phenylhydrazine, gives a dihydropyrazole.[52]

In the third example, the phenylthiosemicarbazide intermediate condenses with benzaldehyde; and the benzal derivative, in hot formic acid, forms a phenyliminothiadiazolone. Since alkyl and aryl isothiocyanates form thiosemicarbazides readily with hydrazine, the substituents in the imido group of the thiodiazolone can vary widely; and since other aldehydes such as salicyl, cinnamyl, and *m*-nitrobenzaldehyde can be used in place of benzaldehyde, the aryl substituent at C_2 can vary also. In example 4, phenylthiosemicarbazide itself undergoes ring closure, when heated with formic acid (formylation occurs) until dissolved. Similarly, acetyl chloride and benzoyl chloride will introduce the acetyl or benzoyl radical in place of the formyl and cause ring closure.

In the fifth example, a hydrazide is converted to a benzal-derivative, which, by mild oxidation, undergoes the customary ring closure to give a 1,3,4-oxadiazole. In the sixth example, a formyl group is extruded from the hydrazine by the action of an aryldiazonium chloride in dilute sodium hydroxide solution. Ring closure then produces an N-aryl-substituted tetrazone. The reaction takes place with phenyl, *p*-tolyl-, and *p*-nitrophenyl-diazonium chlorides. Diacetyl- can be used in place of diformylhydrazine. Extrusion of an acetyl group by reaction of an aryldiazonium chloride has been observed before in the Japp-Klingemann synthesis of indoles. The diformyl or diacetyl hydrazine is not, of course, a prerequisite for preparing the tetrazole compound, since that product can be produced from the monohydrazide.

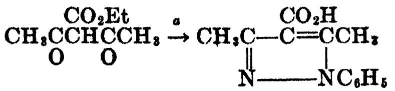
In the seventh example, an imino ether, prepared as described for the reactions in Fig. 3, reacts with hydrazine; and the monohydrazine product, with benzoyl chloride, forms a benzoyl derivative and, thence, gives a triazole. Hot acetic anhydride, instead of benzoyl chloride, produces a triazole also. The reaction with the iminoether hydrochloride may also be repeated on the other end of the hydrazide, *i.e.*, on the monohydrazidine, with formation of a dihydrazidine, $H_2NC(R){=}N{-}N{=}C(R)NH_2$, which then loses ammonia and forms a triazole. A reaction of the same monohydrazidine intermediate with nitrous acid to form a tetrazole has been given in Fig. 3, example 6.

These preparations can, in general, be repeated with phenylhydrazine. For example, the acetyl derivative of ethyl acetoacetate gives, after alkaline hydrolysis of the initial product, 1-phenyl-3,5-dimethylpyrazole-4-carboxylic acid.[53]

---

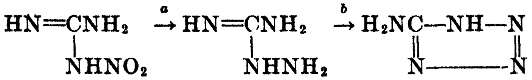
[52] WANTZ, *J. Am. Chem. Soc.*, **57**, 205 (1935).

[53] KNORR, *ibid.*, **20**, 1096 (1887).

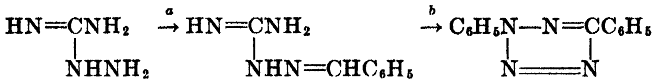


[a] $C_6H_5NHNH_2$, alcoholic KOH.

In addition to the processes listed in Fig. 8, there are a number of other condensations that may be classified as the work of hydrazine derivatives or of open-chain compounds that contain two adjacent nitrogen atoms. For example, the reduction of nitroguanidine gives guanylhydrazine.[54] Nitrous acid then forms an aminotetrazole.

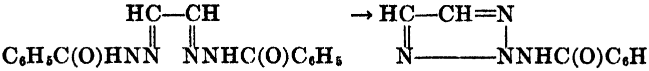


The guanylhydrazine will condense with benzaldehyde, and the benzal derivative is convertible to 2,5-diphenyltetrazole[55] by successive treatments with phenyldiazonium chloride and concentrated nitric acid.

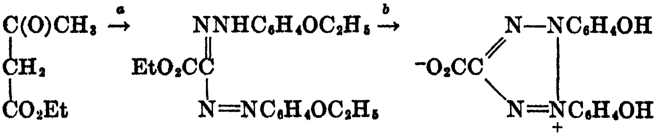


[a] C_6H_5CHO. [b] $C_6H_5N_2Cl$ forms $HN{=}C(NH_2)NHN{=}C(C_6H_5)N{=}NC_6H_5$, HNO_3 eliminates the $HN{=}C(NH_2)$ portion while closing the ring.

Benzhydrazide forms a dibenzoylosazone with glyoxal; and this compound by mild oxidation and hydrolysis gives a 2-benzoylaminotetrazole.[56]



Azo systems can be used in these preparations also. Ethyl acetoacetate and *p*-ethoxydiazonium chloride in alkaline solution form ethyl di-*p*-ethoxyphenyl-formazylformate with extrusion of the acetyl group (compare pages 102 and 374). Amyl nitrite and hydrochloric acid convert



[a] Reaction with two molecules of *p*-ethoxydiazonium chloride. [b] $C_5H_{11}ONO$ + HCl, fuming HCl at 140 to 146°C.

this compound at 0° to the carbethoxy tetrazolium salt and at room temperature to the carboxytetrazolium salt. Hot fuming hydrochloric acid eliminates the two ether groups and gives the dipolar product. Permanganate oxidation of this last compound gives the unsubstituted tetrazole.[57]

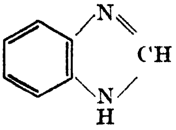
---

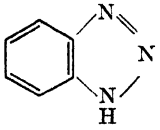
[54] Thiele, *Ann.*, **270**, 1 (1892); **287**, 233 (1895); *cf.* Lieber and Smith, *Chem. Rev.*, **25**, 213 (1939).

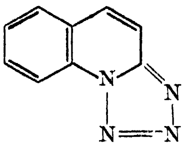
[55] Wedekind, *Ber.*, **30**, 449 (1897).

[56] v. Pechmann and Bauer, *ibid.*, **42**, 667 (1909); Stollé, *ibid.*, **42**, 1047 (1909); Dimroth, *Ann.*, **325**, 90 (1904).

Preparation by Oxidation of Condensed Systems.—Oxidation of condensed azole compounds by permanganate usually results in breaking the aromatic ring. The product is a dicarboxylic acid of the azole compound. A few systems that have been cleaved in this manner are shown below.

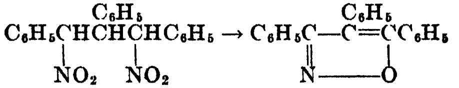






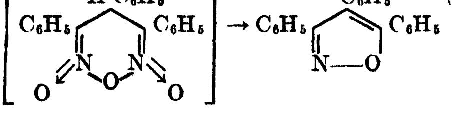
Ref. 58 59 60

Isoxazoles from Nitro Compounds.—Nitro groups activate adjacent methylene groups, undergo hydrolysis, act as oxidizing agents, and suffer reduction. It is not surprising, therefore, that nitro compounds with or without aldehydes form isoxazoles readily. For example, phenylnitromethane with benzaldehyde forms triphenylisoxazole.[61] Since aldehydes condense readily with active methylene groups, this process may begin with the formation of $C_6H_5C(NO_2){=}CHC_6H_5$. Another molecule of phenylnitromethane adds to the olefin bond, and the dinitro product is then assumed to undergo an intramolecular oxidation and reduction with hydrolytic elimination of nitrous acid, enolization, and ring closure.



$$C_6H_5\underset{NO_2}{CH}\overset{C_6H_5}{CH}\underset{NO_2}{CH}C_6H_5 \rightarrow C_6H_5C{-}\overset{C_6H_5}{C}{=}CC_6H_5 \quad (\text{ring } N{-}O)$$

The first steps in this series are very similar to the combination of aldehyde, active hydrogen, and enolizable ketone which is present in the Hantzsch synthesis of dihydro pyridines (see page 187). If the similarity is maintained, an unstable oxadiazine, shown below, would form by loss of water and then decompose to the stable azole by loss of nitrous acid.



---

[57] v. Pechmann and Wedekind, *Ber.*, **28**, 1688 (1895).

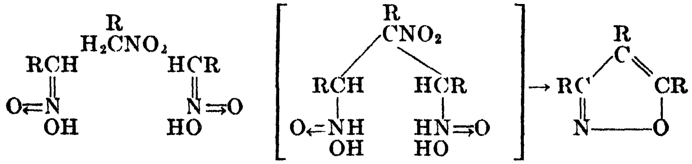
[58] Bamberger and Berle, *Ann.*, **273**, 311. 338 (1893); Burian, *Ber.*, **37**, 701 (1904).

[59] Bladin, *ibid.*, **26**, 545, 2737 (1893).

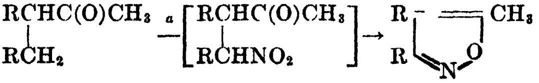
[60] Marckwald and Meyer, *ibid.*, **33**, 1885 (1900).

[61] Kohler, *J. Am. Chem. Soc.*, **46**, 1733 (1924); Meisenheimer, *Ann.*, **446**, 205 (1926); **495**, 247 (1932).

Some nitro compounds condense with themselves, by elimination of water, nitric acid, and hydroxyl amine, and form an isoxazole.[62] Nitroethane and primary nitropropane undergo such a reaction, but nitromethane and secondary nitropropane do not. The mechanism of the process is unknown, but a plausible beginning[63] would be the addition of one active methylene group across the aci form of two nitroalkanes. The remaining steps could be loss of 2 molecules of water to give a dinitroso compound, enolization to a dioxime, removal of the tertiary NO_2 group by hydrolysis to nitric acid, hydrolysis of one oxime to give hydroxylamine, enolization, and ring closure.



Isoxazole derivatives are also formed by nitration of the acetyl derivative of diethyl succinate.[64] This process likewise appears to involve loss of water from enol forms.



$R = -CO_2C_2H_5$.

[a] Fuming HNO_3 at 15 to 20°.

PREPARATION OF AZOLONES

Theoretically, any process capable of producing an azole will produce an azolone, if an acid or ester is used in place of the aldehyde or keto group. A diversified collection of illustrations is shown in Fig. 9. The well-known condensations that occur in the first example are an exact counterpart of those with 1,3-dialdehydes or ketones shown in Fig. 8. The combination of addition and condensation that hydrazine undergoes with acrylic acid in example 2 parallels the reaction with the propargyldiethylacetal in Fig. 8. The reaction of the diketene and the hydrazine in example 3 is of the same general type although lacking in the hydroxyl group. The thiocyanate in example 4 is obtained from the reaction of an alkali thiocyanate with an α-chloro-ester and recalls the α-chloroketones and aldehydes employed as reagents in the reactions described in Fig. 4. Addition of hydrochloric acid, hydrogen sulfide, or water leads to a 2-chloro-, mercapto-, or hydroxy-4-thiazolone, respectively.

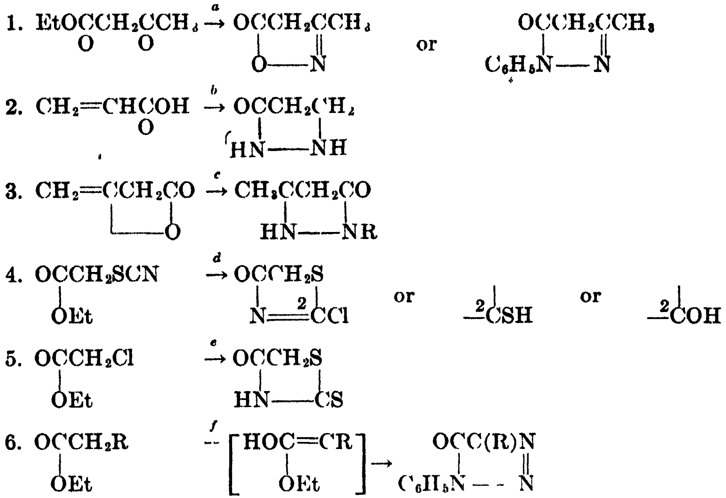
---

[62] Dunstan and Goulding, *J. Chem. Soc.*, **77**, 1262 (1900); Ssokolow, *J. Russ. Phys. Chem. Soc.*, **18**, 282 (1886).

[63] Lippincott, *J. Am. Chem. Soc.*, **62**, 2604 (1940).

[64] Schmidt and Widmann, *Ber.*, **42**, 1879 (1909).

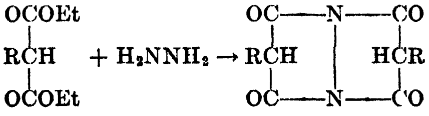
The reaction of the α-chloro ester with ammonium dithiocarbamide in example 5 also appears very similar to those shown in Fig. 4. The addition of phenylazide to the ester in example 6, on the other hand, has no resemblance to the changes such as are in Fig. 5, unless an enolization of the ester, ordinarily not observed, takes place during the reaction.



[a] H_2NOH[65] or $H_2NNHC_6H_5$,[66] respectively. [b] H_2NNH_2[67] [c] $R{=}C_6H_4SO_3H$. Reaction with $H_2NNHC_6H_4SO_3H$.[68] [d] HCl, H_2S, or H_2O, respectively.[69] [e] $NH_2C(S)SNH_4$.[69] [f] $C_6H_5N{=}N{\rightarrow}N$.[70] $R{=}CH_3$ or better CO_2Et.

FIG. 9.—Some processes for preparing azolones.

Condensations sometimes give novel products. For example, the reaction of disubstituted malonic esters with hydrazine gives the expected diketopyrazole system; but if the ethyl malonate is monosubstituted only, the product is a bicyclic compound, a 2,6-dialkyltetraketopyrazo[1,2-*a*]-pyrazole.[71] Benzil, subjected to the action of urea in the presence of potassium hydroxide, undergoes the familiar rearrangement to benzilic



References to Fig. 9

[65] HANTZSCH, *ibid.*, **24**, 495 (1891).

[66] KNORR, *Ann.*, **237**, 137 (1887); *Ber.*, **16**, 2597 (1883); **17**, 549 (1884); **18**, 311 (1885).

[67] v. ROTHENBERG, *J. prakt. Chem.* [2], **51**, 16 (1895).

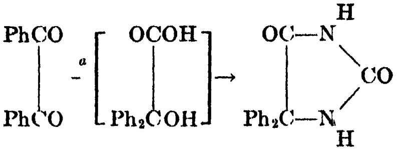
[68] BOESE, JR., *Ind. Eng. Chem.*, **32**, 16 (1940).

[69] MIOLATI, *Ann.*, **262**, 61 (1891); ANDREASCH and ZIPSER, *Monatsh.*, **24**, 499 (1903); **25**, 159 (1904).

[70] DIMROTH, *Ber.*, **35**, 1029, 4041 (1902); *Ann.*, **335**, 1 (1904); **338**, 143 (1905).

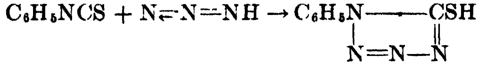
[71] CONRAD and ZART, *Ber.*, **39**, 2282 (1906); DOX, *J. Am. Chem. Soc.*, **54**, 3674 (1932).

acid, which, with urea, forms diphenylhydantoin.[72] Addition of hydrazoic acid to phenylisothiocyanate gives 1-phenyl-5-mercaptotetrazole[73]



[a] KOH + $H_2NC(O)NH_2$.

rather than the tautomeric thiazolone. The compound is acidic enough to be titrated by alkalies with phenolphthalein as an indicator.



$$C_6H_5NCS + N{=}N{=}NH \rightarrow C_6H_5N\text{——}CSH\ (N{=}N{-}N)$$

Although it is necessary to use an acid or ester to produce an azolone, it does not follow that acids will invariably give azolones. For example, if an α-amino acid is heated with acetic anhydride and sodium acetate and the acetylated product is treated with phosphorus pentachloride, the product is an oxazole,[74] not an oxazolone. In this instance, a second

TABLE 1.—OXAZOLES OBTAINED FROM AMINO ACIDS

Acid	Oxazole	B.p., °C.	M.p. of Chloro-aurate, °C.	M.p. of Picrate, °C.
Glycine	2,5-Dimethyl-	117°	152°	124°
d,l-Alamine	2,4,5-Trimethyl-	134	93	115
d,l-Valine	2,5-Dimethyl-4-isopropyl-	150	Oil	122
l-Leucine	2,5-Dimethyl-4-isobutyl-	180	Oil	92
d,l-Phenylalanine	2,5-Dimethyl-4-benzyl-	267		
l-Tyrosine	2,5-Dimethyl-4-p-hydroxybenzyl-[a]	161	103–4	Oil
d-Glutamic	2,5-Dimethyl-4-propionic acid-[b]	130°/12 mm.[c]		118[c]

[a] An alternative name is *p*-hydroxyphenyl(2,5-dimethyloxazolyl-4)-methane.
[b] An alternative name is β-(2,5-dimethyloxazolyl-4)-propionic acid.
[c] Methyl ester.

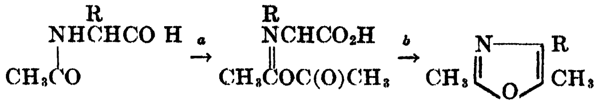
---

[72] BILTZ and RIMPEL, *Ber.*, **41**, 1384 (1908).

[73] STOLLÉ and STRITTMATTER, *J. prakt. Chem.* [2], **133**, 60 (1934); FREUND and HEMPEL, *Ber.*, **28**, 74 (1895).

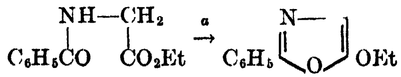
[74] WREDE and FEUERRIEGEL, *Z. physiol. Chem.*, **218**, 129 (1933).

acetylation is superimposed on the first. Ring closure to an oxazole then follows. Approximately 1 g. of oxazole is obtained per 5 g. of amino acid used. A large number of amino acids have been converted to oxazoles by this method (see Table I). Protein, similarly treated, yields the same oxazole as is obtained from lysine.[75] l-Aspartic acid, cystine, and tryptophan do not undergo this change.



[a] Second acetylation. [b] PCl₅ effects ring closure by dehydration and also causes decarboxylation.

If the second acetyl group had not been introduced into the amino acid, the condensation would probably have taken the normal course. Ethyl hippurate, for example, forms 2-phenyl-5-ethoxyoxazole.[76]

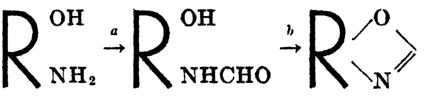


[a] PCl_5 on a water bath.

PREPARATION OF BENZAZOLES

Methods of synthesis of benzazoles may be divided into four general classes: the first and most common one from *o*-substituted anilines, a second from ortho-free anilines, a third from *o*-halogen substituted benzene compounds by elimination of hydrogen halide, and a fourth from *o*-nitro aromatic compounds. This classification does not cover every instance known of benzazole formation, but it illustrates the more common ones and gives a picture of the great tendency toward ring formation.

From *o*-Substituted Anilines.—Examples of this first class are shown in Fig. 10. The majority of these condensations, if not all, proceed through intermediate steps. For example, formic acid, heated with *o*-aminophenol, gives 2-formaminophenol, and this compound, when heated further, loses water in the manner familiar for 1,4 dienol compounds.[77]



[a] HCO_2H. [b] Heat.

Similarly an *ortho*aminophenol and cyanogen bromide in the presence of alkali form a phenylurea. Stronger alkali then causes ring closure.[85]

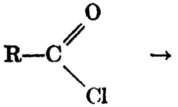
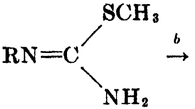
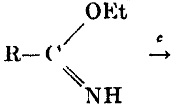
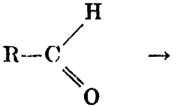
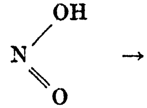
---

[75] WREDE, *ibid.*, **206**, 146 (1932).

[76] KARRER and GRÄNACHER, *Helv. Chim. Acta*, **7**, 763 (1924).

[77] BAMBERGER, *Ber.*, **36**, 2052 (1903).

SUBSTITUENT ATTACHED TO THE 2-POSITION IN THE

Reagent 1 2 3	*Benzoxazole from $\mathrm{R}\begin{matrix}\mathrm{OH}\\ \mathrm{NH_2}\end{matrix}$	Benzothiazole from $\mathrm{R}\begin{matrix}\mathrm{SH}\\ \mathrm{NH_2}\end{matrix}$	Benzimidazole from $\mathrm{R}\begin{matrix}\mathrm{NH_2}\\ \mathrm{NH_2}\end{matrix}$	Benzazole from $\mathrm{R}\begin{matrix}\mathrm{CH_3}\\ \mathrm{NH_2}\end{matrix}$
	R[78]	R[79,a]	R[80]	(Heterocyclic compounds are obtained with some of these reagents, but the products have only one hetero atom.)
 [b]	NHR[81]	NHR[82]		
 [c]	R[82]	R[82]		
	R[82]	R[83,d]	R[84,e]	
$R-C\equiv N$ →	R[82]	R[82]		
$N\equiv C-Br$ →	NH_2[85]	....	NH_2[85]	
	....	(A benzothiadiazole)[86]	(A benzotriazole)[87]	(An indazole)[88]
$S=C=S$ →	SH[89]	SH[90]		

1. Atom or group that becomes the substituent at the 2-position.
2. Atom that becomes part of the ring at the 2-position.
3. Components that participate in the reaction.

[a] The zinc salt of the thio compound is used with advantage in this condensation. The anhydride, acid, or nitrile and hydrochloric acid may be used also in this reaction.

[b] The reagent is the methyl ether obtained from the reaction of methyl sulfate with a substituted isothiourea, such as that from thiocarbanilide or other similar compound.

[c] The reagent is an imino ether, prepared from the reaction of a nitrile with an anhydrous alcohol in the presence of hydrochloric acid or from the silver salt of an amide with an alkyl iodide.

[d] A thiazoline should be the primary product of the condensation with aldehydes. Aerial oxidation occurs too rapidly to permit isolation of such an intermediate. In the case of 2-amino-4-chlorothiophenol, however, such intermediates are stable enough to be isolated as crystalline compounds. Mild oxidation by potassium ferricyanide converts them to benzothiazoles.

[e] Ammoniacal cupric acetate is used as an oxidizing agent.

FIG. 10.—Synthesis of benzazoles from *o*-substituted anilines.

---

[78] LADENBURG, *Ber.*, **9**, 1524 (1876).

[79] HOFMANN, *ibid.*, **12**, 2359 (1879); BOGERT and SNELL, *J. Am. Chem. Soc.*, **46**, 1308 (1924).

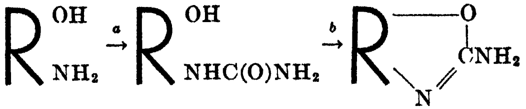
[80] PHILLIPS, *J. Chem. Soc.*, 172, 2393 (1928); WUNDT, *Ber.*, **11**, 826 (1878); DAINS, *ibid.*, **35**, 2496 (1902); GRASSI-CHRISTOLDI and LOMBARDI, *Gazz. chim. ital.*, **25**, I, 224 (1895).

[81] DECK and DAINS, *J. Am. Chem. Soc.*, **55**, 4986 (1933).

[82] WHEELER, *Am. Chem. J.*, **17**, 397 (1895); HOFMANN, *Ber.*, **13**, 1223 (1880); **20**, 2551 (1887).

[83] HOFMANN, *ibid.*, **13**, 1223 (1880); BOGERT and NAIMANS, *J. Am. Chem. Soc.*, **57**, 1529 (1935);

The formation of this intermediate is typical,



Large R = $C_6H_3AsO(OH)_2$. The arsenic acid radical is para to the oxygen atom in the heterocyclic product.

[a] Cyanogen bromide and aqueous sodium hydroxide. [b] A 20 per cent sodium hydroxide solution.

in part of the general behavior of amines with cyanogen bromide in that metathesis first occurs with formation of a cyanamide, not isolated. In the synthesis of the oxazole, water adds to this cyanamide and forms

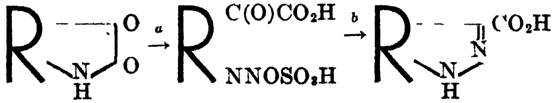
$$RNH_2 + CNBr \rightarrow RNHCN + HBr$$

the phenylurea (also called the carbamido) product mentioned above; in the reaction with other amines, a molecule of the amine adds and forms a guanidine derivative.

$$RNHCN + RNH_2 \cdot HBr \rightarrow (RNH)_2C{=}NH \cdot HBr$$

The necessary intermediates for these preparations are made by well-recognized reactions. *o*-Aminophenol is derived from *o*-nitrophenol. *o*-Aminothiophenol is readily obtained by the reaction of *o*-nitrochlorobenzene with sodium disulfide, followed by reduction of the disulfide with zinc dust and acetic acid. The zinc mercaptide can be used directly in the reactions with benzoyl and other chlorides, or can be recovered as the mercaptan after treating with hydrogen sulfide or strong hydrochloric acid.[79] *o*-Phenylenediamine is obtained by reduction of *o*-nitroaniline.

Formation of some indazoles may be included in this class. Isatin, for example, undergoes ring opening, and then a reduction and condensation, with formation of an indazole-3-carboxylic acid,[91] somewhat after the manner of the better known Pfitzinger synthesis (page 273).



[a] The isatin is dissolved in dilute sodium hydroxide and treated with sodium nitrite and then with cold dilute sulfuric acid. The *o*-diazophenylglyoxylic acid is stable only in cold dilute acid solution. [b] $SO_2 + SnCl_2$. The intermediate hydrazine probably forms.

Lankelma and Sharnoff, *ibid.*, **53**, 2654 (1933).

[84] Weidenhagen and Weeden, *ibid.*, **71**, 2347 (1938).

[85] Stickings, *J. Chem. Soc.*, 3131 (1928); Pierron, *Ann. chim.* [8], **15**, 191 (1908); Noelting, *Ber.*, **37**, 2556 (1904).

[86] Jacobson, *ibid.*, **21**, 3104 (1888).

[87] Ladenburg, *ibid.*, **9**, 219 (1876).

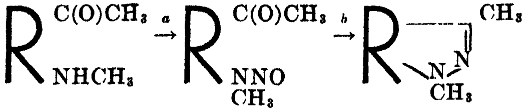
[88] Barclay, Campbell, and Dodds, *J. Chem. Soc.*, 113 (1941); Jacobson and Huber, *Ber.*, **41**, 660 (1908).

[89] Dünner, *ibid.*, **9**, 465 (1876).

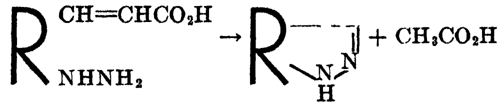
[90] Hofmann, *ibid.*, **20**, 1788 (1887).

[91] Shad, *Ber.*, **26**, 216 (1893).

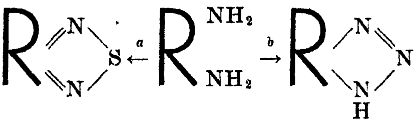
N-Methyl-2-aminoacetophenone, treated with nitrous acid followed by reduction, gives 3-methylindazole.[92] 2-Hydrazinocinnamic acid easily loses acetic acid and changes to indazole.[93]



[b] Zn dust + HOAc.

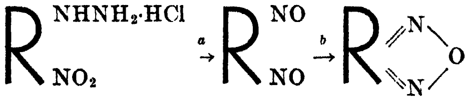


There are some preparations, as indicated below, which are observed only with compounds that contain two amino groups, ortho to each other.



[a] Reaction with SO_2.[94] A similar reaction with SeO_2 gives the selenium analogue. [b] Reaction with $^{+}N_2C_6H_4SO_3^{-}$. The nonheterocyclic product of this reaction is $H_2NC_6H_4SO_3H$.[95]

Similarly, an ortho dioxime,[96] when steam distilled from dilute alkali solution, gives a benzofurazan. The necessary dioxime can be prepared by the following sequence of reactions:



[a] HNO_2 followed by quick heating on a water bath. This process depends on the formation of, a phenylazide, $NO_2C_6H_4N_3$, that melts at 53° but decomposes above 70°.

[b] Reduction of the dinitroso compound to the dioxime followed by treatment with hot alkali. The reducing agent is hydroxyl amine and alkali (compare Wolff-Kizhner reduction). Stronger reducing agents such as stannous chloride, ammonium sulfide, or zinc dust, form *ortho*phenylene diamine.

From Anilines or Other Compounds with a Free Ortho Position.—In condensations of this type, the reagent must supply the two atoms necessary to complete the heterocyclic ring. Among these processes are the well-known preparation of captex and dehydrothiotoluidine from aniline and from *p*-toluidine by use of sulfur and carbon disulfide or of sulfur, respectively. An intermediate thiophenol probably forms.

---

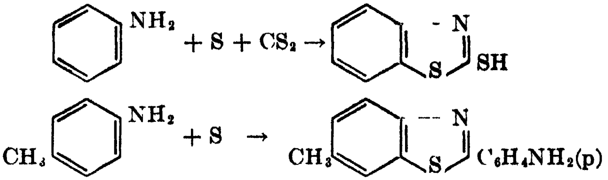
[92] Fischer and Tafel, *Ann.*, **227**, 336 (1885).

[93] Fischer and Kuzel, *ibid.*, **221**, 280 (1883).

[94] Hinsberg, *Ber.*, **22**, 862, 2895 (1889).

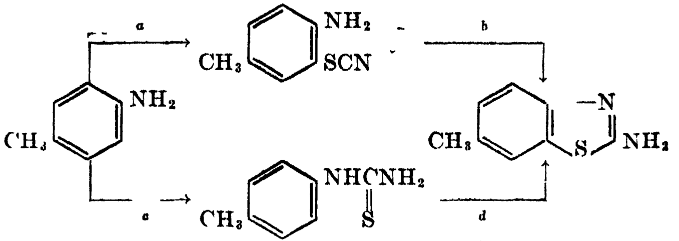
[95] Griess, *ibid.*, **15**, 2195 (1882).

[96] Zincke, *J. prakt. Chem.* [2], **53**, 340 (1896); Zincke and Schwarz, *Ann.*, **307**, 28 (1898).



Methylaniline boiled with sulfur similarly forms a benzothiazole.[97]

When *p*-toluidine (and also *p*-chloro, nitro-, acetyl- or other substituted aniline) is treated with sodium thiocyanate in acetic acid with bromine, substitution (thiocyanation) takes place in the ortho position. Alkali then closes the ring.[98] When the toluidine is treated with the thiocyanate in concentrated sulfuric acid, condensation occurs. Ring closure of the tolylthiourea is then accomplished by bromine or thionyl chloride.[99] The same 2-aminobenzothiazole results in either case.

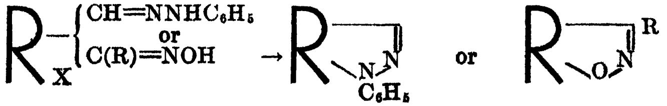


^{a} NaSCN + HOAc + Br_2. ^{b} NaOH. ^{c} NaSCN + H_2SO_4. ^{d} $SOCl_2$ or Br_2.

p-Phenetidine and copper thiocyanate also give 2-aminobenzothiazole,[100] presumably by way of thiocyanation.

Condensations such as occur in the sulfur fusion of anilides or the oxidation by potassium ferricyanide of thioanilides fall within this class. Benzothiazoles are formed. Phenylisothiocyanate adds alcohol, and the product by oxidation forms a 2-ethoxybenzothiazole.

From Appropriately *o*-Substituted Bromo- or Chloro-benzenes.—The conventional elimination of hydrobromic or hydrochloric acid under the influence of alkali can be employed for syntheses of some benzazoles.[101] Preparation of an indazole and a 1,2-benzisoxazole, depending on the group adjacent to the halogen, is shown below.



---

[97] Möhlau and Klopfer, *Ber.*, **21**, 3164 (1898).

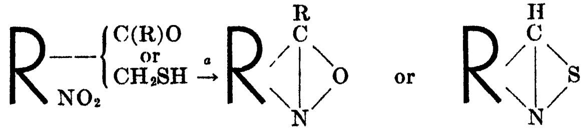
[98] Hunter, *J. Chem. Soc.*, **127**, 2023 (1925); Brewster and Dains, *J. Am. Chem. Soc.*, **58**, 1364 (1936).

[99] Allen and van Allan, *Org. Syntheses*, **22**, 16 (1942).

[100] Kaufman and Kuckler, *Ber.*, **67**, 944 (1934).

[101] Cathcart and Meyer, *ibid.*, **25**, 3291 (1892); Meyer, *ibid.*, **26**, 1250 (1893).

From *o*-Nitro Aromatic Compounds.—Reduction of an appropriate ortho nitro compound often leads directly to a benzazole. *o*-Nitrobenzaldehydes or *o*-nitrophenyl ketones give anthranils[102] by such a method; *o*-nitrobenzylmercaptan yields 2,1-benzisothiazole.[103]



[a] Sn + HCl. The bridge formula is used in this case in place of the alternative *o*-quinoid structure.

PHYSICAL PROPERTIES AND THE STRUCTURE OF THE AZOLES

Solubility in Water.—In general, the physical properties of the azoles reflect the result of combining the ammono aldehyde system of pyridine with the ether, thio ether, and imide systems present in furan, thiophene, and pyrrole, respectively. The effect of the former is greater than that of the latter. For example, pyridine is soluble in water in all proportions; the other monoheterocyclic compounds are slightly soluble; the corresponding azoles, even some of the methyl homologues, dissolve appreciably in water, some in all proportions. There are, of course, variations among the different classes of azoles. Isoxazoles as a rule are less soluble than the corresponding oxazoles. Isoxazole[104] itself is soluble in six volumes of water and 3-methyl-,[104] 5-methyl[3]-,3,5-dimethyl,[105] and 3,4,5-trimethylisoxazoles[62] are difficultly soluble in water. 2,4-Dimethyl[106] and 2,5-dimethyloxazole[4] are, on the other hand, easily soluble in water. This difference between the two series of isomers reflects the difference in solubility that exists between oximes and amides (oxazoles may be regarded as a tautomeric form of cyclic amides) in that the former are less soluble than are the latter.

Similarly, the solubility of the thiazoles in water may be compared with that of the pyridines. Pyridine and the three picolines are miscible in all proportions in water; thiazole[107] is very hygroscopic, and 2-methyl[14] and 4-methyl-thiazole[108] are miscible in all proportions.

---

[102] FRIEDLÄNDER and HENRIQUE, *Ber.*, **15**, 2105 (1882); FRIEDLÄNDER and SCHREIBER, *ibid.*, **28**, 1382 (1895); HELLER, *ibid.*, **36**, 2766, 4178 (1903); BAMBERGER, *ibid.*, **48**, 537 (1915).

[103] GABRIEL and POSNER, *ibid.*, **28**, 1027 (1895); GABRIEL and STELZNER, *ibid.*, **29**, 162 (1896); BAMBERGER, *ibid.*, **42**, 1667 (1909).

[104] CLAISEN, *ibid.*, **36**, 3665 (1903); **42**, 65 (1909).

[105] DUNSTAN and DYMOND, *J. Chem. Soc.*, **59**, 411 (1891).

[106] SCHUFTEN, *Ber.*, **28**, 3071 (1895).

[107] POPP, *Ann.*, **250**, 275 (1888); WILLSTÄTTER and WIRTH, *Ber.*, **42**, 1908 (1909).

[108] ARAPIDES, *Ann.*, **249**, 24 (1888).

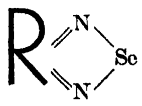
The 2,4-,[109] 2,6-[110] 2,5-,[111] and 3,5-dimethylpyridines[112] are more soluble in cold than in warm water. In the case of 2,6-lutidine,[110] the lower critical solution temperature is 45°; the upper is 163.5°. Similarly, 2,4-dimethyl-,[14] 2,5-dimethyl-,[4] 2,4,5-trimethyl-,[113] 2-methyl-4-ethyl-,[113] and 4-methyl-2-ethyl-[15] thiazole are more soluble in cold than in warm water. 2,4-Dimethylthiazole[14] is miscible in all proportions in ice water but separates into two layers when warmed. This peculiarity of a closed solubility curve is not limited to compounds that contain the C═N function, for piperidine[110] acts similarly.

The benz compounds are, in general, less soluble in water than the monocyclic compounds, but benzimidazole is easily soluble and indazole (benzopyrazole) crystallizes from hot water. All are, however, soluble in cold strong mineral acids (HCl) from which they may often be recovered, merely by dilution, since the basicity of many of these compounds is usually so slight that hydrolysis occurs easily. Oxazoles may be decomposed (the ring opened) by such treatment.

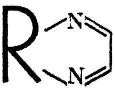
Phenyl-substituted monocyclic azoles are in general somewhat similar to the benzazoles. They usually dissolve in cold concentrated mineral acid and precipitate when the solution is diluted.

Azoles with an imide hydrogen are apt to be soluble in water or alcohol. If this hydrogen atom is substituted by an alkyl or phenyl group, the compounds become sparingly soluble in water. The solubility of these compounds in an organic solvent such as benzene follows the converse rule of slight solubility for N-unsubstituted azoles, and high solubility for N-substituted compounds.

Odors.—The odors of the isoxazoles,[104] the oxazoles, and thiazoles[14] are frequently similar to those of the corresponding compounds in the pyridine series. This similarity extends to the benz series. Benzothiazole and benzoisothiazole have the odor of quinoline, benzoselenodiazole[94] resembles quinoxalin,[114] and benzothiadiazole[94] has an intensive odor.



Benzoselenazole



Quinoxalin

The phenyl and benz substituents are noteworthy, however, for their wide variety of, and occasionally, very pleasant odors. Some of these

---

[109] Hantzsch, *Ber.*, **17**, 2908 (1884).

[110] Flaschner, *J. Chem. Soc.*, **95**, 668 (1909).

[111] Errera, *Ber.*, **34**, 369 (1901).

[112] Dürkopf and Göttsch, *ibid.*, **23**, 111 (1890).

[113] Roubleff, *Ann.*, **259**, 253 (1890).

[114] Michaelis, *ibid.*, **274**, 262 (1893).

TABLE II.—ODORS OF SOME AZOLE COMPOUNDS

Compound	M.p. °C	B.p. °C/mm.	Odor	Ref.
5-*n*-Amylisoxazole	....	....	Aromatic	115
5-*n*-Hexylisoxazole	....	....	Aromatic	115
3,4,5-Trimethylisoxazole	....	....	Peppermint	116
3-Phenylisoxazole	....	253/757	Aromatic	117
4-Phenylthiazole	52	273	Diphenylamine	107,108
5-Phenylthiazole	45–46	....	Funguslike	5
2-Benzylthiazole	Oil	....	Aromatic	83
4-Methyl-2-phenylthiazole	....	279/724	Fruity	15
4-Methyl-2-phenylselenazole	....	283/737	Fruity	18
4,5-Dimethyl-2-phenyloxazole	50–55	....	Caraway	118
5-Methyl-2-phenylthiazole	....	283.5/750	Quinoline	3
2-Methyl-5-phenylthiazole	81°	....	Pyridine	3
2,4-Dimethyl-5-phenylthiazole	51–52	....	Jasmine	5
2,5-Dimethyl-5-phenylthiazole	Oil	271/755	Rose	5
2-Methyl-5-*p*-tolylthiazole	81–82	....	Leek	119
Anthranil	Oil	100.4/15	Characteristic	102
Thioanthranil	Oil	242/748	Anthracene	120
Benzoxazole	30.5	182.5	Anthracene	77
Chloroanthranil	79–79.5	....	Anthracene	121
2-Chlorobenzothiazole	Oil	248	Aromatic	122
3-Methylanthranil	....	111/10	Anthranil	123
2-Methylbenzoxazole	Oil	200/201	Characteristic	78
2-Methylbenzothiazole	....	238	Pyridine	124
2-Ethylbenzothiazole	....	252	Aromatic	122
4-Methylbenzothiazole	....	252	Quinoline	125
6-Methylbenzothiazole	....	255	Pleasant	125
2,5-Dimethylbenzoxazole	....	218/748	Characteristic	126
4,6-Dimethylbenzothiazole	....	....	Disagreeable	127
2,4,6-Trimethylbenzoxazole	28.5	234-236	Penetrating	128
2,5,6-Trimethylbenzoxazole	93–94	....	Characteristic	129
5-Chloro-2-methylbenzoxazole	53	218-220	Pleasant	130
2-Phenylbenzothiazole	112–113	>360	Tea roses	79
3-Phenylanthranil	52–53	....	Characteristic	131
3-Phenyl-1,2-benzisoxazole	84	....	Sweetish	132
2,1-Naphthoxazole	63.5–64	....	Roses (weak)	133

---

[115] MOUREU and DELANGE, *Compt. rend.*, **138,** 1341 (1904).

[116] SSOKOLOW, *J. Russ. Phys. Chem. Soc.*, **18,** 282 (1886); *Ber.*, **19R,** 540 (1886), Julius Springer, Berlin, 1937.

[117] CLAISEN, see BEILSTEIN, "Handbuch der Organischen Chemie," Julius Springer, Berlin, 1918.

[118] DIELS and RILEY, *Ber.*, **48,** 897 (1915).

[119] RUDENBURG, *ibid.*, **46,** 3555 (1913).

[120] BAMBERGER, *ibid.*, **42,** 1647 (1909).

[121] BAMBERGER and LUBLIN, *ibid.*, **42,** 1676 (1909).

[122] HOFMANN, *ibid.*, **13,** 8 (1880).

[123] BAMBERGER and ELGER, *ibid.*, **36,** 1611 (1903).

[124] JACOBSON, *ibid.*, **19,** 1067 (1886).

[125] RASSOW and REIM, *J. prakt. Chem.* [2], **93,** 214 (1916).

[126] NOELTING and KOHN, *Ber.*, **17,** 351 (1884).

[127] GUDEMAN, *ibid.*, **21,** 2549 (1888).

[128] v. AUWERS and BORSCHE, *ibid.*, **48,** 1698 (1915).

[129] DIEPOLDER, *ibid.*, **44,** 2498 (1911).

[130] UPSON, *Am. Chem. J.*, **32,** 13 (1904).

[131] BAMBERGER and LINDBERG, *Ber.*, **42,** 1723 (1909).

[132] JAEGER, *Z. Kryst.*, **44,** 50 (1908).

[133] FISCHER, *J. prakt. Chem.* [2], **73,** 419 (1906).

compounds are listed in Table II in the order of alkyl-substituted monocyclic azoles, phenyl-substituted monocyclic azoles, alkyl benzazoles, phenyl benzazoles, and naphthazoles. The melting and boiling points are included in the table since the majority of these compounds will not be mentioned elsewhere in this text.

Boiling Points.—Replacement of a double methine group by sulfur causes as little difference between the boiling points of pyridine and thiazole as it does between benzene and thiophene (see Table III).

TABLE III.—EFFECT OF REPLACEMENT OF DOUBLE METHINE BY SULFUR GROUP

	B.p.	M.p.	Density
Thiophene	84	−40	1.0844
Benzene	80.1	5.51	0.8794
Thiophene − benzene	3.9	....	0.2050
Thiazole	116.8	....	1.198
Pyridine	115.3	−42	0.982
Thiazole − pyridine	1.5	....	0.216

Replacement of oxygen by sulfur raises the boiling point. In monocyclic compounds, this change decreases as the molecular weight or boiling point increases. For bicyclic compounds, the amount is greater than for monocyclic.

Oxygen series	B.p., °C.	Sulfur series	B.p., °C.	Increase
Furan	32	Thiophene	84	52
2,4-Dimethyloxazole	108	2,4-Dimethylthiazole	145[a]	37
2,5-Dimethyloxazole	118	2,5-Dimethylthiazole	153	35
2,5-Dimethyl-1,3-4-oxadiazole	179	2,5-Dimethyl-1,3,4-thiadiazole	203	24
Benzoxazole	182.5	Benzthiazole	230	69

[a] Boiling point at 719 mm.

As a general rule, the boiling point of an isoxazole, a cyclic oxime, is higher than that of an oxazole. For example, all the dimethylisoxazoles and the trimethylisoxazoles (Table IV) have higher boiling points than do the dimethyl- or trimethyl-oxazoles. The differences amount to 20 or 30°.

The above relationships are made the basis for the arrangement of Table IV. The boiling points, in general, increase from left to right; although it is possible that the lower boiling oxadiazoles have boiling points less than the thiazoles. The value for the unknown parent member of the oxazole series is estimated to be near 70°. That for other compounds in these series could be approximated also. The table is incomplete, but the trends in boiling point are readily discerned.

Azoles with an imide system have boiling points (see Table V) higher than other azoles, a fact that can be attributed to hydrogen bonding such as occurs in water, alcohols, and phenols. Hydrogen bonding in the pyrazoles is illustrated[134] by the simple bimolecular formula shown below. For some of the other azoles, a termolecular or higher form would be needed.

TABLE IV.—BOILING POINTS[a] OF SOME AZOLE COMPOUNDS ARRANGED TO SHOW THE INFLUENCE OF STRUCTURE ON THE BOILING POINTS OF SOME ANALOGUES AND ISOMERS

Substituent	Oxazole, °C.	Isoxazole, °C.	Thiazole, °C.	1,3,4-Oxadiazole, °C.	1,2,3-Thiadiazole, °C.	1,3,4-Thiadiazole, °C.
None	[70]	95.5	116.8	....	157/742	
2-Methyl	...	.....	128/729			
3-Methyl	...	118.5				
4-Methyl	...	.....	133			
5-Methyl	...	122.1	....	....	184	
2,4-Dimethyl	108	.....	145.5/719			
2,5-Dimethyl	118	.....	153	179	....	203
3,4-Dimethyl	145	.....	....	156/744[b]		
3,5-Dimethyl	...	142				
4,5-Dimethyl	150					
2,4,5-Trimethyl	134	.....	167/717			
3,4,5-Trimethyl	...	171				
2-Phenyl	228	.....	269/732			
3-Phenyl	...	250				
4-Phenyl	222	.....	273			
5-Phenyl	...	247				

[a] Boiling point near 760 mm. unless otherwise given.

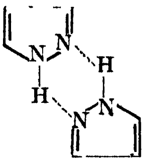
[b] The 1,2,3- instead of the 1,3,4-oxadiazole.

TABLE V.—BOILING POINTS OF IMIDE-CONTAINING AZOLES

Monocyclic compounds	M.p., °C.	B.p., °C.	Bicyclic compounds	M.p., °C.	B.p., °C.
Pyrazole	70	185	Indazole	146.5	269–270/743
Imidazole	90	256	Benzimidazole	170	300
1,2,3-Triazole	23	203	1,2,3-Benztriazole	99–100	
1,2,4-Triazole	120–121	260			
Tetrazole	155–156				

---

[134] HAYES and HUNTER, *J. Chem. Soc.*, 1 (1941).



When the imide hydrogen is replaced by a methyl group, the boiling point is lowered. In all cases, a compound with an alkyl or phenyl substituent on the nitrogen atom boils lower than the isomeric compound with the substituent on carbon[134] (see Table VI).

TABLE VI.—BOILING POINTS OF SUBSTITUTED PYRAZOLES AND IMIDAZOLES

Pyrazole substituent	B.p., °C.	Pyrazole substituent	B.p., °C.	Imidazole substituent	B.p., °C.
None	188	1,3,4-Trimethyl	160	None	255–256
1-Methyl	127	1,3,5-Trimethyl	170	1-Methyl	198
3-Methyl	205	1,4,5-Trimethyl	177	1-Ethyl	206
4-Methyl	205	3,4,5-Trimethyl	233	2-Methyl	268
1,3-Dimethyl	136	1,3,4,5-Tetramethyl	193	4-Methyl	263
1,5-Dimethyl	153	1-Phenyl	246	2-Ethyl	268
3,4-Dimethyl	222	3-Phenyl	313	1,2-Dimethyl	206
3,5-Dimethyl	218	....	...	1,4-Dimethyl	199

Melting Points.—Monocyclic azoles that contain no imide group are, in general, liquids. Identification must be made by means of such solid derivatives as the mercuric chloride, chloroplatinate, picrate compounds. The unsubstituted bicyclic compounds, too, are more apt to be liquids than solids.

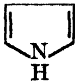
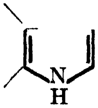
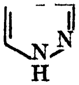
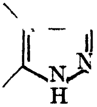
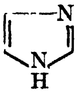
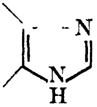
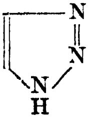
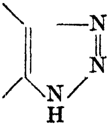
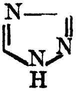
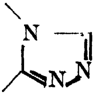
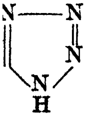
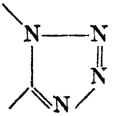
As might be expected, the azoles with an imide system have definite melting points. In general, the increase in melting point caused by the benz increment is approximately 78° (see table on page 392); this value agrees very well with the 74.8° difference in melting point between benzene and naphthalene.

In the case of pyridotetrazole[135] (the last compound in the bottom line), and probably also in that of pyrido[2,1-*c*]-s-triazole (next to the last compound), the same melting-point increase fails to appear, a fact understandable in that there is no longer an imide hydrogen atom present to provide hydrogen bonding.

Structure and the Positions of the Double Bonds.—The fine structure of the benzazole and higher condensed systems has received considerable attention, particularly from the standpoint of the fixation of the double

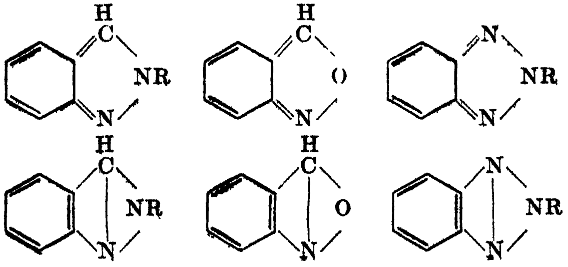
---

[135] FARGHAR and FURNESS, *ibid.*, **107**, 695 (1915).

Monocyclic series			Bicyclic series			Benz increment	
	Mp. °C.	Bp °C.		Mp. °C.	Bp. °C.	Mp. °C.	Bp. °C.
	[−27][a]	130		52.5	254	....	124
	70	185		146.5	270[b]	76.5	85
	90	256		170	300	80	44
	23	203		100	....	77	
	120	260					
	155	...		159	....	4	

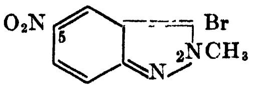
[a] Estimated value. [b] Boiling point at 743 mm.

bonds. For example, the 2-substituted indazoles, anthranils, and triazoles might be represented by either of two forms shown, respectively, below.

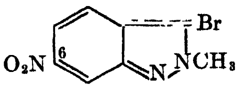


The structures in the upper line have an ortho quinoid arrangement; those in the lower line have a benzoid one, accompanied by a bridge in the heterocyclic part. Undoubtedly, resonance hybrids are present, yet arguments have been advanced for one type or the other as a preferred state. For example, many of the compounds are colorless, a circumstance regarded as being in disagreement with the general properties of ortho quinones. Moreover, polynuclear aromatic systems, according to the principle of Fries,[136] tend to assume the state of individual benzene rings. On the other hand, the idea of a four-membered ring as a preferred state is difficult to accept. Refractivity measurements[137] do not support such an opinion.

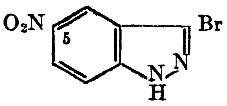
A novel chemical approach to the problem[86] has been made in the case of the 3-chloronitrobenzimidazole. A nitro group activates bromine only if placed so that the sequence of double and single bonds will be the same as in *o*- or *p*-nitrobromobenzene. Hence 5-nitro- (but not 4- or 6-nitro-) 3-bromo-2-methylindazole has a halogen atom that can be removed by piperidine. The activation would, obviously, not apply in such force when the 2-position is unsubstituted because the benzoid structure could predominate. The data supporting these conclusions are given in Table VII. The results suggest an ortho quinoid structure.



Active bromine



Inactive bromine



Slightly active bromine

TABLE VII.—ACTIVATION OF THE BROMINE ATOM IN 3-BROMO-SUBSTITUTED NITROINDAZOLES

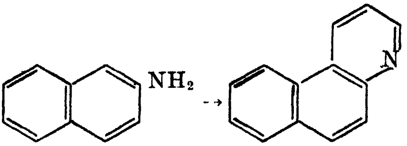
3-Bromoindazole	Per cent bromine removed by piperidine		
	45°/1 hr.	45°/24 hr.	95°/3 hr.
4-Nitro-	..	0	
4-Nitro-1-methyl	0	0	
4-Nitro-2-methyl-	0	0	
5-Nitro-	0	4	
5-Nitro-2-methyl-	2	30	45
5-Nitro-1-methyl-	0	0	0
6-Nitro-	0	0	0
6-Nitro-1-methyl-	0	0	0 2(?)
6-Nitro-2-methyl-	0	0	0

---

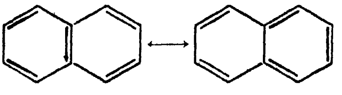
[136] FRIES, WALTER, and SCHILLING, *Ann.*, **516**, 248 (1935).

[137] v. AUWERS, *ibid.*, **437**, 70 (1924); **527**, 291 (1937); MEISENHEIMER and DIEDRICH, *Ber.*, **57**, 1715 (1924).

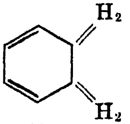
The problem of fixed double bonds has been studied also from the viewpoint of whether the adjacent heterocyclic ring permits the benzene nucleus to exhibit benzoid or naphthoid properties. If benzoid, the double bond will be freely oscillating and the position of substitution will not be critical; if naphthoid, the double bonds and the position taken by an entering group will be fixed. For example, in a Skraup synthesis the position of ring closure in a benzene ring is on either side of the amino group (benzoid type); but in naphthalene it is on one side only (naphthoid type), and an angular rather than a linear benzoquinoline (see below) results.



For condensed azole systems, the problem of naphthoid and benzoid can be referred to the stability of dihydrobenzene and the dihydroazoles. For example, naphthalene exists primarily in the resonance form (*a*) rather than (*b*), and this less stable form may be regarded as equivalent to dihydrobenzene (*c*), which is unstable and reverts readily to benzene.

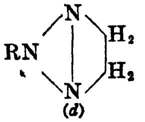


(*a*) (*b*)

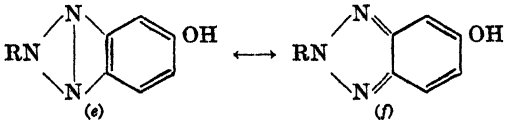


(*c*)

If, therefore, the dihydroazole compound is unstable or does not form, the corresponding benzazole compound would be of the naphthoid type; if stable, the bicyclic system would be of the benzoid type. C, C-Dihydrotriazoles (*d*) are not known to exist. Hence, 2-substituted-5-hydroxybenzotriazoles, for which two resonance forms (*e*) and (*f*) can be written, should (and do) show the reactions peculiar to a β-naphthol; from this circumstance the argument stems that the double bonds in the aromatic ring of the triazole should be located as are those in the corresponding ring in the naphthol.[138] In short, the resonance form on the left (in *e*) would be favored. On the other hand, dihydroimidazole (*g*) is a very stable compound. Hence, 5-hydroxybenzimidazole can function readily in either resonance position (*h*), and either side of the hydroxy group is active and participates in reactions.



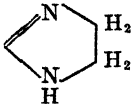
(*d*)



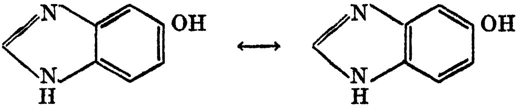
(*e*) (*f*)

---

[138] FRIES, *Ann.*, **389**, 305 (1912); **454**, 121 (1927).



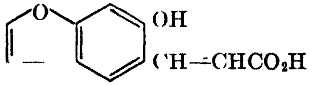
(g)

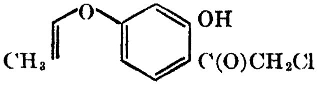


(h)

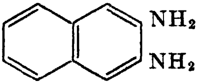
The reactions used in these tests are recorded in Table VIII. At the head of each column, a compound of the pure naphthoid type (naphthalene) and pure benzoid type (tetrahydronaphthalene), respectively, is listed. The results with heterocyclic compounds indicate that benzotriazoles are definitely naphthoid, diazoles are less so, and tetralin and benzofuran are completely benzoid. Benzimidazole, benzothiazole, and benzisothiazole are mainly benzoid but show some analogies with naphthalene. Indazoles exhibit these analogies a little more clearly.

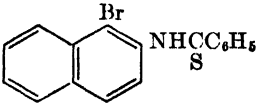
Although a sharp demarcation in types is not always found, the practical significance of these results is shown by the failure (*a*) of the Skraup synthesis to produce a linear benzoquinoline from β-aminonaphthalene or (*b*) of ring closure to occur in the two compounds given below,





which involve attempted formation of a coumarin and coumaranone system. The seeming exception shown by 2,3-diaminonaphthalene, which reacts very easily with *o*-phenylene diamine, and by thiobenz-(bromonaphthyl)amide, which condenses to a thiazole product, can be explained on the ground that the heterocyclic systems thus produced are





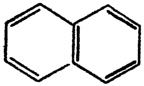
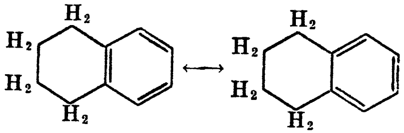
not such as to interfere with a naphthoid character of the naphthalene portion of the molecule.

That the principles[139] discussed are not inviolate is shown by the fact that 1-chloro-2-naphthylamine will undergo a Skraup synthesis to give a linear compound, although the general rule is to eliminate a halogen atom such as bromine, and yield an angular compound.

These studies of the position at which a reaction occurs are important. It does not follow, however, that because all naphthoid compounds have a fixed double bond at one part of the ring, all compounds that have a fixed double bond at that corner must be naphthoid and have a double bond also where the two rings are joined. The structure represented earlier by (*f*) likewise fulfills all requirements for a comparative rigid benzotriazole system; and the work on the 3-bromonitroindazoles, men-

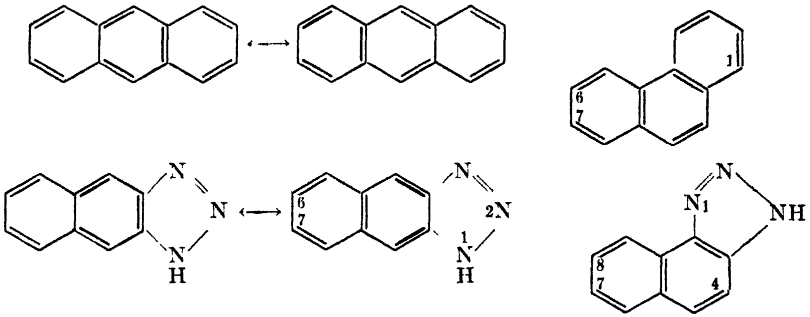
[139] Fries, *ibid.*, **516**, 285 (1935).

TABLE VIII.—REACTIONS THAT TYPIFY NAPHTHOID AND BENZOID STRUCTURES

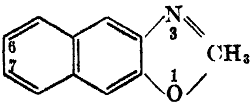
 Naphthoid character	 Benzoid character
1. β-Amino compounds form aminoazo compounds β—$C_{10}H_7NH_2 + RN_2X \rightarrow RN_2C_{10}H_6NH_2$	The amine and a diazonium salt from a diazoamino compound, a criterion of doubtful value $C_6H_5NH_2 + RN_2X \rightarrow RN_2NC_6H_5$
2. Ring closure takes place on one side only of the β-amino group in the Skraup synthesis	Ring closure in the Skraup synthesis takes place on either side of the β-amino group
3. β-Hydroxy compound, with α-position blocked will not couple in the free ortho position	β-Hydroxy derivatives couple with diazonium salts in either free ortho position
4. Nitration and halogenation of the parent compound occurs only in the alpha position	Nitration and halogenation occur in either alpha or beta position
5. Halogenation of a β-hydroxyl compound gives a keto halide or an ortho quinone	Halogenation takes place on both sides of a β-hydroxy group to give dibromo derivatives
6. Benzylidene derivatives of β-amino compounds form acridine derivatives readily by refluxing in alcoholic solution	Benzylidene derivatives of amines form acridine compounds with difficulty by heating to 200°

tioned earlier, shows that the bicyclic system can be represented properly as an ortho quinoid benzene derivative.

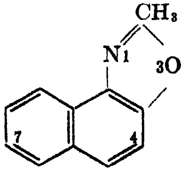
The comparison of anthracene and phenanthrene with the corresponding linear and angular naphthotriazoles confirms the aromatic-like character of the triazole ring. For example, the molal heat of combustion[136] of anthracene is 7 kg.-cal. higher than that of phenanthrene; that of linear naphthatriazole is 3.4 kg.-cal. higher than that of the angular isomer. In general, the high reactivity of anthracene is reflected in the behavior of the linear heterocyclic system. The linear form is reduced to a 4,9-dihydro compound[140] by sodium amalgam in alcohol, and to a 5,6,7,8-tetrahydro product by catalytic (Pt) hydrogen. Chlorine or bromine puts halogen atoms in its 4,9-positions, exactly as these reagents do at the meso positions of anthracene. The hydrogenated or chlorinated derivatives yield the yellow-colored *lin.*-naphthatriazole-4, 9-quinone when oxidized by sodium dichromate. The angular isomer is not hydrogenated under conditions similar to those used above.



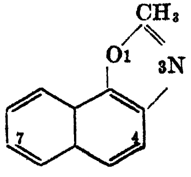
This remarkable similarity with the corresponding aromatic hydrocarbons is consistent with the naphthoid character of the benzotriazoles. Such a relationship is found only in part with other heterocyclic systems. The molal heats of combustion of the first two naphthoxazoles shown below are approximately equal, that of the third is about 8 kg.-cal. lower. Toward concentrated sulfuric acid the linear form is more reactive than the other two.



Naphth[2,3]oxazole
M.p. 87.5
B.p. 310



Naphth[1,2]oxazole
Liquid
312

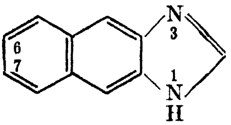


Naphth[2,1]oxazole
41.5
302

---

[140] The numbering system is one given in "The Ring Index" (Patterson and Capell) although it does not emphasize the similarity which these triazole compounds have to anthracene and phenanthrene.

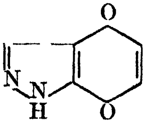
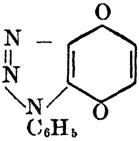
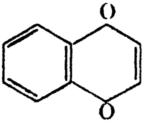
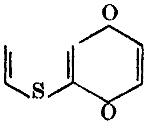
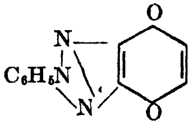
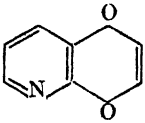
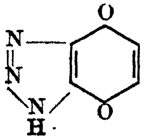
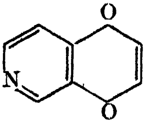
Linear naphimidazole (m.p. 221°) lacks the reactivity of an anthracene compound, for it is not reduced by sodium amalgam or catalytic hydrogen under conditions that are successful with the angular naphthotriazole.[136]



Oxidation by sodium dichromate and boiling dilute sulfuric acid gives the expected 4,9-quinone.

Fieser has studied the problem of bond position in condensed systems by the method of *reduction potential*.[141] For example, the reduction potential of α-naphthoquinone is 224 mv. lower than that of *p*-benzoquinone, and that of α-naphthoquinone is 220 mv. lower than that of *o*-benzoquinone. In other words, the reactivity of one of the quinonoid ethylenic linkages is dampened when it becomes, at the same time, part of another ring system; the greater the lowering, the greater the resistance to change from a quinoid to benzoid structure. If an attached heterocyclic system causes a lowering, the double bond between the two rings would be regarded as correspondingly more stable. The compound with the maximum lowering should, therefore, have the highest naphthoid character. Table IX summarizes the results.

TABLE IX

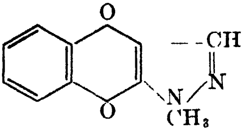
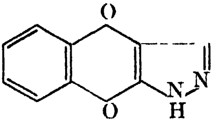
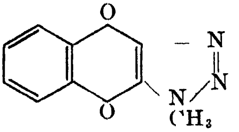
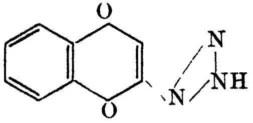
	−240		−176
	−231		−156
	−228		−142
	−189		−135

---

[141] FIESER, *J. Am. Chem. Soc.*, **48,** 1097 (1926); FIESER and MARTIN, *ibid.*, **57,** 1841, 1844 (1935).

Only the condensed pyrazole system exceeds naphthalene in reduction potential. The triazole system approaches naphthalene. The thiophene and pyridine systems have the least effect.

The comparison between indazoles and triazoles, shown below, suggests that the unsubstituted triazole has a different structure than does the 1-methyl derivative. It does not show the nature of the difference. If the bonds of the benzoquinone system are regarded as intact, the only possible formula will have a bridge.

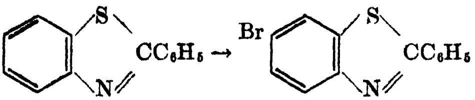
	E		E
	0.160 volt		0.155 volt
	0.235 volt		0.435 volt

CHEMICAL PROPERTIES

The chemical, like the physical, properties are, by and large, a resultant of the effects of the groups present in the ring and the resonance that creates stability to the ring structure. For example, the oxazole is a combination of the oxygen atom of furan with the ammonoaldehyde of pyridine, so that a cyclic imino ester, sometimes called an imino ether, results. The group influence of the ether oxygen atom, so pronounced in the case of furan, is submerged in the ester combination, and the properties of the oxazoles lean more to the pyridine than to the furan side. The chemistry of the monoheterocyclic compounds provides, therefore, a useful guide toward that of the systems with two or more hetero atoms, provided due regard is paid to the manner in which the groups involved affect each other in alicyclic systems and to the powerful effect that resonance can play in stabilizing the ring. Although it is sometimes difficult to trace the individual effects of the groups, the discussion of chemical properties, notably substitution, addition, base and acid relationships, ring opening, and side-chain reactivity, will be based on the general principle that the group behavior sets the pattern for the reactions of the various azoles.

Substitution Reactions.—Substitution will occur but is not common. Usually, substituted azoles are derived by synthesis. Since oxazoles and isoxazoles are combined furan and pyridine systems, with the latter predominating, it is not surprising that chlorine forms an intermediate product with 3-methyl-, 5-methyl-, or 3,5-dimethyl-isoxazole, similar to the formation of perbromides of pyridine; but that, unlike the pyridine compound, this perhalide, under the influence of heat and light, decomposes to hydrogen chloride and a 4-chloroisoxazole.[142] Substitution also takes place in 3,5-dimethylisoxazole[143] which yields a 4-sulfonic acid derivative with chlorosulfonic acid.

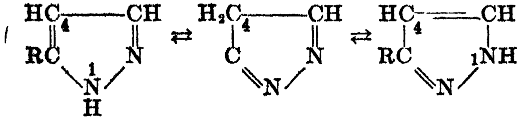
Thiazole, which is to pyridine as thiophene is to benzene, is the least reactive of all azoles toward substituting agents. At ordinary temperatures, bromine forms only a perbromide. It requires the severity of treatment at 250 to 400° over pumice for bromination to occur. 2-Bromothiazole only is formed.[144] Formation of addition products between benzothiazole and bromine is the rule.[145] When 2-phenylbenzothiazole is brominated, the perbromide first formed decomposes in hot acetic acid. Bromination then occurs in the benz ring in the position para to the nitrogen atom.[146]



Although thiazole itself is not nitrated, 2,5-dimethylthiazole forms a 4-nitro product, 2,4-dimethylthiazole a 5-nitro compound, and 4-methylthiazole a nitro product of unknown position when treated with nitric-sulfuric acid mixture. 2,5-Dimethylthiazole yields also a 4-sulfonic acid derivative.[147]

The completeness of the shift from the thiophene to the pyridine type[14] is well illustrated by the fact that thiazole gives no indophenine test with isatin and sulfuric acid and gives no color with phenanthraquinone, although this test is given by some other azoles.

Pyrazole is like pyrrole in that an imide hydrogen atom is part of a ketimine-enimine system (see page 62). The problem is complicated by the presence of a second nitrogen atom which competes for the hydrogen. The ketimine-enimine tautomerism, shown below, however, produces the same methylene compound, irrespective of which nitrogen atom is involved in the imide function. The methylene group is also



---

[142] Quilico and Fusco, *Rend. inst. lombardo sci.*, **69**, 439 (1936); *C.A.*, **32**, 7454 (1938).

[143] Quilico and Justoni, *Gazz. chim. ital.*, **70**, 1 (1940); *C.A.*, **34**, 2843 (1940).

[144] Wibaut and Jansen, *Rec. trav. chim.*, **53**, 77 (1934); Wibaut, *Ber.*, **72**, 1708 (1939).

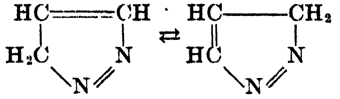
[145] Hunter, *Chem. News*, **129**, 125 (1924).

[146] Bogert and Abrahamson, *J. Am. Chem. Soc.*, **44**, 826 (1922).

[147] Nagazawa, *J. Pharm. Soc. Japan*, **60**, 433 (1940); *C.A.*, **35**, 458 (1941).

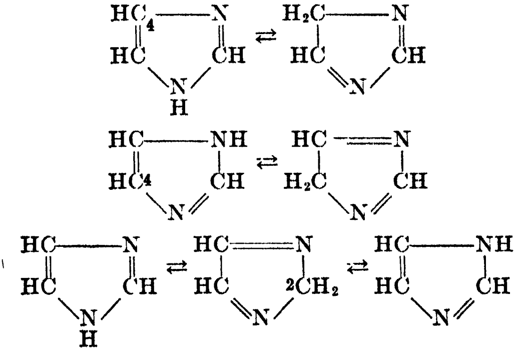
flanked by two ammono-aldehyde functions, which activate it as would two carbonyl groups. Hence the 4-position is particularly active. Bromine, nitric acid, hydroxylamine, and nitrous acid attack the pyrazole system readily at C_4.

Two other tautomeric forms of pyrazole can exist, but in neither is the methylene group activated by the equivalent of a carbonyl group.



The combination of an olefin and an azo lacks the influence of two ammono-aldehyde systems. Hence the C_3 positions are comparatively inactive.

Similar arguments show the absence of a predominantly active position in imidazole. 1,3-Enimization produces one of two possible methylene groups, depending on which nitrogen atom is the starting position for the tautomeric change. 1,5-Enimization, however, places the methylene group at C_2, irrespective of which nitrogen is considered. In spite of this common terminus of the 1,5-tautomerizations, the methylene group at C_2 has no monopoly in reactivity, because it is activated by two —N═C— groups, which have a comparatively weak influence, whereas that on the other carbon atoms is flanked by one —N═C— and the more potent —C═N— group. The net result is that C_2, C_4, and C_5 are approximately equivalent. Bromination or iodination introduces halogens on all the carbon atoms. The imide hydrogen atom is also replaceable, and a tetraiodoimidazole[148] forms. Nitric-sulfuric acid mixture introduces a nitro[149] group in the 4(5)-position. Benzenediazonium chloride gives 2-phenylazoimidazole.[150]



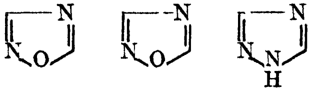
---

[148] PAULY and GUNDERMANN, *Ber.*, **41**, 4010 (1908).

[149] RUNG and BEHREND, *Ann.*, **271**, 28 (1892).

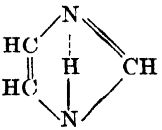
[150] BEHREND and SCHMITZ, *ibid.*, **277**, 388 (1893).

Curiously enough, the two diazoles and the triazole, shown below, give the indophenine test with isatin or phenanthraquinone,[151] a reaction that may be regarded as one of substitution.



Substitution of the imide hydrogen atom in imidazole is not so easy as in pyrrole or pyrazole. Acetyl chloride,[152] acetic anhydride, and benzoyl chloride have no effect. The Grignard reagent gives imidazylmagnesium halide[153] which, in turn, forms a benzoyl derivative[154] with benzoyl chloride. Ethyl chloroformate and phosgene also form N-substituted products with the magnesium compound; acetyl chloride does not.

Such resistance of imidazole has been attributed[153] to an inner hydrogen bonding, a form of chelation, as shown below. This novel structure would undoubtedly alter the reactivity of the hydrogen atom. Hydrogen



bonding unquestionably exists, but the high boiling points of the imidazoles indicate that the bond is more inter- than intra-molecular. The much higher boiling point of the imidazoles as compared with the pyrazoles suggests that the hydrogen bonding in the former is greater, and this view accords with the greater resistance to reaction of the former.

Methylation of imidazole can be accomplished by methyl sulfate in the absence of alkali. If the imidazole is substituted by a nitro group, the basicity is decreased (as judged by the increased solubility in aqueous alkali), and methylation is made easier. In less degree, a bromo group acts similarly. The less basic nitrogen atom is methylated. This nitrogen can be located by an independent synthesis of the methylated imidazole or by degradation. Conversely, groups such as methyl, which increase the basicity, retard methylation. If a nitro and a bromo group oppose each other, as in 4(5)-nitro-5(4)-bromoimidazole, the former has the controlling influence. 1-Methyl-4-bromo-5-nitroimidazole results. Methylation with methyl sulfate and alkali, on the other hand, reduces and sometimes reverses the position of preference;[155] *i.e.*, the more basic nitrogen atom is attacked.

---

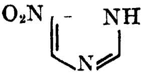
[151] Stollé, *J. prakt. Chem.*, **68**, 130 (1903).

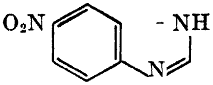
[152] Oddo and Ingraffia, *Gazz. chim. ital.*, **61**, 446 (1931); *C.A.*, **26**, 452 (1932).

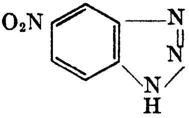
[153] Mingoia, *Gazz. chim. ital.*, **61**, 449 (1931); **63**, 242 (1933); *C.A.*, **26**, 453 (1932); **27**, 4534 (1933).

[154] Oddo and Mingoia, *Gazz. chim. ital.*, **58**, 573 (1928); *C.A.*, **23**, 1639 (1929).

Methylations of benzimidazole[156] and benzotriazole[157] follow the same general rule, *i.e.*, as the basicity is decreased by a nitro group, the methylation is made easier. The nitrogen atoms affected are located by appropriate synthesis and are indicated, together with the corresponding position in nitroimidazole, by the position of the hydrogen in each formula below.







The nitrogen methylated in the monocyclic ring system is the one nearer the nitro group, and the corresponding atom in the benzimidazole is likewise affected. This rule is not followed, however, in the case of 5-nitrobenzotriazole in which the nitrogen affected is para to the nitro group. Possibly the greater tendency of benzotriazoles to have a naphthoid structure has an influence on this reaction.

The results obtained in alkylation of indazoles harmonize, in general, with those found for imidazoles in that methyl iodide or diazomethane acts differently from sodium methoxide. The 2-alkyl derivatives usually result from the use of methyl iodide and possibly, also, of diazomethane, but in the presence of sodium methoxide alkylation occurs at the 2-position also.[158]

Other azoles can be methylated in conventional fashion. The silver salt of tetrazole gives 1-ethyl- and 2-ethyl-tetrazole with ethyl iodide.[159]

The difficulty of substitution in azole systems, particularly in strong acid media where the nitrogen atom forms a salt, can be seen by the results of nitrating compounds that have aromatic rings present also. 2-Phenylthiazole,[160] 1-phenyl-1,2,4-triazole-3-carboxylic acid,[161] 2-phenylimidazole,[162] and 4-phenylimidazole[162] are nitrated in the para position of the aromatic ring, not in the heterocyclic system. A nitro group can be made to enter 4-phenylimidazole[163] at C_5 in the heterocyclic ring, but only after the first aromatic ring is nitrated. Benzothiazole is likewise nitrated in the aromatic portion.[164]

---

[155] Hazeldine, Pyman, and Winchester, *J. Chem. Soc.*, **125**, 1431 (1924); Forsyth and Pyman, *ibid.*, **127**, 574 (1925); *cf.* Ref. 156.

[156] Phillips, *J. Chem. Soc.*, 1143 (1931).

[157] Brady and Reynolds, *ibid.*, 2667 (1930).

[158] v. Auwers and Düesberg, *Ber.*, **53**, 1179 (1920); *cf.* Ref. 155.

[159] Oliveri-Mandala and Passalaqua, *Gazz. chim. ital.*, **43**, II, 471 (1913).

[160] Friedman, Sparks, and Adams, *J. Am. Chem. Soc.*, **59**, 2262 (1937).

[161] Pellizzari, *Gazz. chim. ital.*, **32**, I, 189; *Atti accad. Lincei* [5], **10**, II, 297; **11**, I, 20; *Chem. Cent.* (1902) I, 426, 668, 1164.

[162] Grant and Pyman, *J. Chem. Soc.*, **119**, 1873 (1921); Pyman and Standley, *ibid.*, **125**, 2484 (1924).

Addition Reactions.—The addition reactions, described in this section, include ordinary reduction and additions to the ammono-aldehyde system. The related salt formation (addition to the nitrogen atom only) is discussed under separate title of Bases, Acids, and Salts. Presence of the —C=N function renders azoles, in general, susceptible to the reagents that have such a marked influence on pyridine. The products will be as predicted, save for the modifying influence of the other hetero atom or atoms.

Sodium and alcohol or water is an effective reducing agent for many azoles. Isoxazoles and oxazoles, and occasionally thiazoles, may suffer cleavage (to be discussed later under Ring Opening) during reduction. Many N-aryl-substituted pyrazoles,[165] but not N-unsubstituted compounds, can be reduced to pyrazolins. Pyrazole[166] itself is not reduced by sodium and boiling amyl alcohol. Imidazole is also resistant to sodium and alkali and to sodium amalgam, as well as to zinc and hydrochloric acid, and 60 per cent hydriodic acid and phosphorus.[167] This resistance is not caused by a tendency for the imidazolin to revert to an imidazole, since the 4,5-dihydro compound[168] obtained when ethylene diamine hydrochloride is heated with sodium acetate is stable. The resistance shown by these imide-containing compounds is related possibly to hydrogen bonding.

Zinc and hydrochloric or acetic acid is not so effective as sodium and alcohol for the reduction of thiazole compounds.[169] 3,4,5-Trimethylisoxazole is reduced by zinc and sulfuric acid or by aluminum amalgam and dilute sulfuric in acetic acid, but the ring is simultaneously opened and the products are ammonia and a secondary alcohol.[105,116]

By analogy with pyridine, thiazoles, *e.g.*, 4-methylthiazole,[170] should and do add sodamide. Thiazole can be aminated also by hydroxylamine[171] by a process that may involve addition, followed by elimination of water, as suggested by Skraup. Benzoxazole undergoes a similar amination. Some 2-formaminophenol is simultaneously formed. Benzimidazoles, 1-phenylpyrazole, 2-phenyl-1,2,3-triazole, 4,5-diphenylbenzoxazole, and 6-dimethylaminothiazole are unaffected by hydroxylamine.

---

[163] PCHIAI and KAZUNORI, *J. Pharm. Soc. Japan*, **60**, 313 (1940); *C.A.*, **35**, 458 (1941).

[164] JACOBSON and KWAYSSU, *Ann.*, **277**, 237 (1893).

[165] BALBIANO, *Gazz. chim. ital.*, **18**, 354 (1888); *cf.* Ref. 53.

[166] BUCHNER, FRITSCH, PAPENDIECK, and WITTER, *Ann.*, **273**, 214 (1893).

[167] WYSS, *Ber.*, **10**, 1364 (1897).

[168] OESTERREICH, *ibid.*, **30**, 2254 (1897).

[169] SCHATZMANN, *Ann.*, **261**, 6 (1891).

[170] OCHIAI and NAGASAWA, *Ber.*, **72**, 1470 (1939).

[171] SKRAUP, *Ann.*, **419**, 1 (1919).

Base, Acid, and Salt Relationships.—Azoles are *bases* of varying degrees of strength that form salts with acids and alkyl halides. Thiazole is a weaker base than pyridine (K_B at 25° = 3.3×10^{-12} and 2.3×10^{-9}), respectively. Accordingly, salts of phenylthiazole are more dissociated by cold water than are salts of pyridine; and salts of thiazole in general show an acid reaction.

Azoles with an imide hydrogen atom are less basic than ammonia or hydrazine (K_B at 25° = 1.8×10^{-5} and 1.6×10^{-6}), respectively, in accordance with the properties of the iminophenol or acid function present. For example, pyrazole and 1,2,4-triazole have basic dissociation constants[172] of 3×10^{-12} and 2×10^{-12}, respectively. Imidazole is a cyclic amidine and, in keeping with the strong basic properties of amidines,[173] is the most basic ($K_B = 1.2 \times 10^{-7}$) of all the imide-containing azoles, more basic even than pyridine. The contrast between imidazole and the isomeric pyrazole is apparent from the fact that the hydrochloride, nitrate, and sulfate salts of the latter are too unstable to be isolated, but the mineral acid salts of the former can be obtained by evaporation of the acid solution.

Imidazole nitrate[174] melts at 118°. Although mineral salts of pyrazole are not readily obtained, the oxalate and picrate salts (m.p. 192 and 159 to 160°, respectively) can be isolated. Aqueous pyrazole solutions are neutral to litmus.

Imino hydrogen atoms have, of course, *acidic properties*. The Grignard reagent and imidazole or pyrazole[153] form magnesyl derivatives. In liquid ammonia,[175] imidazoles form metallic salts with alkali and alkaline-earth metals.

Silver salts are precipitated readily with imidazole, pyrazole, 1,2,3-triazole,[176] 1,2,4-triazole,[2,177] and tetrazole.[178] 1,2,3-Triazole[178] liberates hydrogen with sodium in ether solution. Calcium hydroxide dissolves in a triazole solution. Tetrazole[177] is acid enough to redden litmus paper and to conduct an electric current in water or ammonia. The aqueous solution of its sodium salt shows a neutral reaction and deposits crystals of sodium tetrazole when cooled or evaporated. The barium salt is also easily dissolved by water.

The alkyl halide salts of the azoles undergo the expected reactions.

[172] BUCHNER, *ibid.*, **273**, 218 (1893).

[173] SEN and RAY, *J. Chem. Soc.*, 646 (1926).

[174] DEDICHEN, *Ber.*, **39**, 1831 (1906).

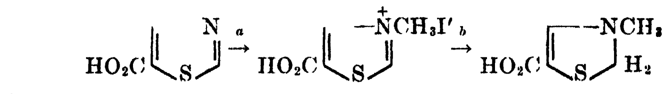
[175] FRANKLIN and BERGSTROM, *Chem. Rev.*, **16**, 315 (1936).

[176] BALTZER and v. PECHMANN, *Ann.*, **262**, 320 (1891).

[177] STRAIN, *J. Am. Chem. Soc.*, **49**, 1566, 1995 (1927).

[178] THIELE and INGLE, *Ann.*, **287**, 233 (1895).

For example, reduction of thiazole methiodide by hydrogen over platinum gives a pyrazoline.[179]



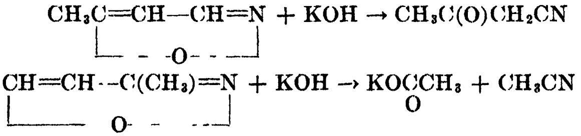
^{a} CH_3I. ^{b} H_2 + Pt.

The typical ring-opening processes, which employ salts, also occur (see next section).

Ring Opening.—Good methods for ring opening are important because the degradation products may serve as clues to the structure of the original compound or as sources of open-chain compounds.

Since azoles may be regarded as cyclic oximes, dioximes, imino esters, iminothio esters, hydrazines, or amidines, depending on whether the types are isoxazoles, furazans, oxazoles, thiazoles, pyrazoles, or imidazoles, respectively, the frequent use of *alkali* as a reagent for ring opening is not surprising. Resistance to such a reagent would depend on the degree to which resonance stabilizes the ring.

If an isoxazole has a substituent at C_5, cleavage[51,104] occurs at the oxygen atom only and a keto nitrile results; if it has a substituent at C_3, cleavage occurs also between C_3 and C_4, and an acid and a nitrile result. In either event, one product is a nitrile, and carbon-carbon cleavage occurs, if necessary for formation of the nitrile.

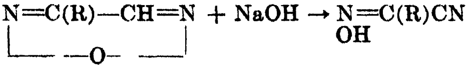


$$CH_3C{=}CH{-}CH{=}N + KOH \rightarrow CH_3C(O)CH_2CN$$

$$CH{=}CH{-}C(CH_3){=}N + KOH \rightarrow KO\underset{O}{C}CH_3 + CH_3CN$$

As might be expected, the first process is so much easier than the second that a mixture of the two isomers, treated with cold sodium ethoxide or alcoholic potassium hydroxide, can be freed of the former.

The same reagent cleaves also the related furazan.[28] A nitrile is again formed.



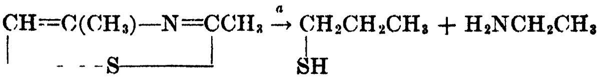
$$N{=}C(R){-}CH{=}N + NaOH \rightarrow \underset{OH}{N}{=}C(R)CN$$

Alkyl thiazoles[180] may be attacked by alkali if reducing or oxidizing conditions are used.[181] Boiling sodium ethoxide, for example, cleaves

---

[179] Erlenmeyer, Epprecht, and v. Mayenburg, *Helv. Chim. Acta*, **20**, 514 (1937).
[180] Schuftan, *Ber.*, **27**, 1009 (1894).
[181] Henrich, *ibid.*, **54**, 2492 (1921).

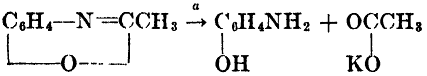
2,4-dimethylthiazole during reduction by sodium and alcohol. Alkylthiazoles are attacked by potassium hydroxide in the presence of potassium hypochlorite.[14]



$$\mathrm{CH{=}C(CH_3){-}N{=}CCH_3} \xrightarrow{a} \underset{\mathrm{SH}}{\mathrm{CH_2}}\mathrm{CH_2CH_3} + \mathrm{H_2NCH_2CH_3}$$

[a] Na + boiling C_2H_5OH.

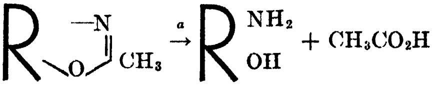
Benz-substituted azoles[78] undergo the same ring opening. Benzoxazoles with an alkyl group in the 2-position are hydrolyzed more readily than those with an aryl group. The product is an amino phenol.



$$\mathrm{C_6H_4{-}N{=}CCH_3} \xrightarrow{a} \underset{\mathrm{OH}}{\mathrm{C_6H_4}}\mathrm{NH_2} + \mathrm{O}\underset{\mathrm{KO}}{\mathrm{C}}\mathrm{CH_3}$$

[a] KOH at 120°.

Acids may sometimes be used to open the ring. Oxazoles[78] are thus cleaved, mere evaporation on a water bath being often sufficient.



[a] Long standing or warming with dilute H_2SO_4.

Pyrazoles[182] and pyrazolines are stable to concentrated hydrochloric acid. Dimethyl pyrazole-3,5-dicarboxylate is, however, readily hydrolyzed by sulfuric acid.[166]

Tetrazole is largely resistant to fuming hydrochloric acid[178,183] at 200°. Concentrated sulfuric acid,[184] however, breaks it to carbon dioxide, nitrogen, and ammonia.

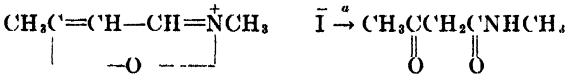
Methiodide salts of azoles are readily attacked by alkali or silver hydroxide. The first step is similar to that in the formation of pyridone. The hydroxyl group moves to the adjacent carbon atom. The final products are those which result from rearrangement of hydrogen atoms and then cleavage to produce stable products. The processes frequently give high yields, so much so, in fact, that Claisen regarded the decomposition of pyrazoles as a preparative method for *s*-hydrazines. Examples of the reaction of some quaternary salts with alkali and also with other related reagents are given below.

---

[182] Curtius and Wirsing, *J. prakt. Chem.* [2], **50**, 531 (1894).

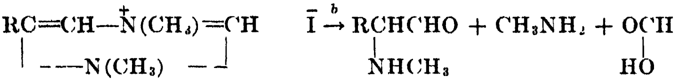
[183] Heller, *Ber.*, **40**, 114 (1907).

[184] Bladin, *ibid.*, **25**, 1412 (1892).



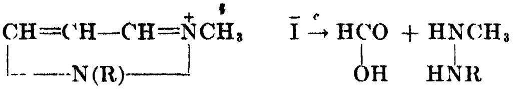
$$\underbrace{CH_3C{=}CH{-}CH{=}\overset{+}{N}CH_3}_{-O-}\quad \bar{I}\xrightarrow{a} CH_3\underset{\underset{O}{\|}}{C}CH_2\underset{\underset{O}{\|}}{C}NHCH_3$$

[a] Cleavage with AgOH.[185]



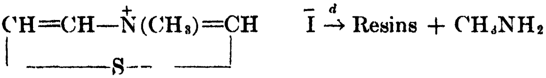
$$\underbrace{RC{=}CH{-}\overset{+}{N}(CH_3){=}CH}_{-N(CH_3)-}\quad \bar{I}\xrightarrow{b} R\underset{\underset{NHCH_3}{|}}{C}HCHO + CH_3NH_2 + O\underset{\underset{HO}{|}}{C}H$$

[b] AgOH.[149, 186]



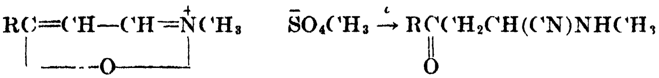
$$\underbrace{CH{=}CH{-}CH{=}\overset{+}{N}CH_3}_{-N(R)-}\quad \bar{I}\xrightarrow{c} H\underset{\underset{OH}{|}}{C}O + H\underset{\underset{HNR}{|}}{N}CH_3$$

[c] Cleavage with KOH.[187]



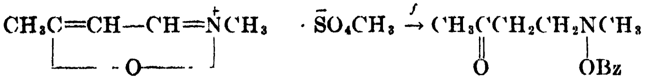
$$\underbrace{CH{=}CH{-}\overset{+}{N}(CH_3){=}CH}_{-S-}\quad \bar{I}\xrightarrow{d} \text{Resins} + CH_3NH_2$$

[d] KOH.[188]



$$\underbrace{RC{=}CH{-}CH{=}\overset{+}{N}CH_3}_{-O-}\quad \overline{SO_4}CH_3\xrightarrow{e} R\underset{\underset{O}{\|}}{C}CH_2CH(CN)NHCH_3$$

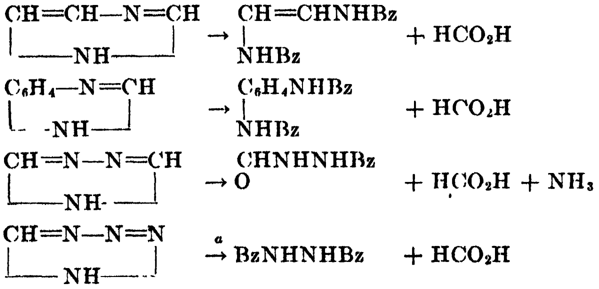
[e] KCN.



$$\underbrace{CH_3C{=}CH{-}CH{=}\overset{+}{N}CH_3}_{-O-}\quad \cdot\,\overline{SO_4}CH_3\xrightarrow{f} CH_3\underset{\underset{O}{\|}}{C}CH_2CH_2\underset{\underset{OBz}{|}}{N}CH_3$$

[f] $C_6H_5CO_2K$.[185]

Benzoyl chloride and alkali (Schotten-Baumann reaction) cleave azoles smoothly, particularly in the case of imidazoles,[58] where a dibenzoyldiamino product results. The reaction is general. 1,2,4-Triazoles and tetrazoles are similarly affected. 1,2,3-Triazoles,[183] however, merely form the N-benzoyl-derivative.



$$\underbrace{CH{=}CH{-}N{=}CH}_{-NH-} \rightarrow \underset{\underset{NHBz}{|}}{CH}{=}CHNHBz + HCO_2H$$

$$\underbrace{C_6H_4{-}N{=}CH}_{-NH-} \rightarrow \underset{\underset{NHBz}{|}}{C_6H_4}NHBz + HCO_2H$$

$$\underbrace{CH{=}N{-}N{=}CH}_{-NH-} \rightarrow \underset{O}{CHNHNHBz} + HCO_2H + NH_3$$

$$\underbrace{CH{=}N{-}N{=}N}_{-NH-} \xrightarrow{a} BzNHNHBz + HCO_2H$$

[a] Na_2CO_3 used instead of NaOH in this reaction.

Since quinoline[189] and benzothiazole[97] react with benzoyl chloride and alkali (in the latter case with ring opening), and since 1-methyl and

---

[185] Claisen, *ibid.*, **45**, 59 (1909).

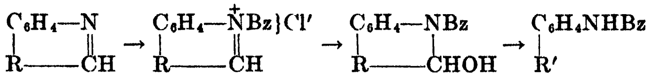
[186] Pinner and Schwartz, *ibid.*, **35**, 2441 (1902).

[187] Knorr and Weidel, *ibid.*, **42**, 3523 (1909).

[188] Mumm and Bergell, *ibid.*, **45**, 3040 (1912).

[189] Reissert, *ibid.*, **38**, 3415 (1905); Mihlan, *ibid.*, **39**, 862 (1906); Friedländer

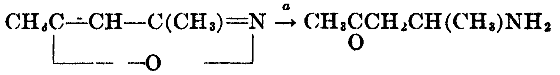
1-ethylimidazole[186] also react with benzoyl chloride and alkali, the reaction is not connected to the imide hydrogen atom, but is probably related to the behavior of methiodide salts with alkali just discussed. The steps in the case of imidazole[190] would be benzoylation of the imide system and then a series of changes identical with those for quinoline or benzothiazole, as shown below in the general equation.



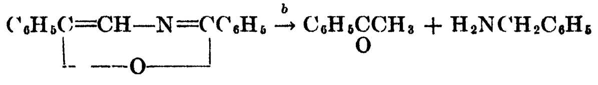
R indicates —CH=CH—, —S—, or —NR—. R′ indicates —CH=CH$_2$, —SH, or —NH$_2$. HCO$_2$H is formed from the carbon atom adjacent to the nitrogen.

Ring opening is not limited to the use of benzoyl chloride and alkali. The acid chlorides of the half esters of oxalic and malonic acids have been used successfully with imidazole.[154] Benzoyl chloride[191] is claimed to be ineffective in some cases where isovaleryl chloride, $(CH_3)_2CHCH_2$-C(O)Cl, will open the ring. In other instances, benzoyl chloride and pyridine have been used in place of the acid chloride and sodium hydroxide. Benzoyl chloride has also opened the ring and formed a diamine with benzimidazolylmagnesium halide.[192]

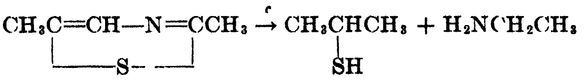
Reductive cleavage frequently takes place when azoles are treated with sodium and alcohol. The products are, in general, the same as with alkali cleavage alone, except that the nitrile system is not eliminated but reduced. A few examples are listed below.



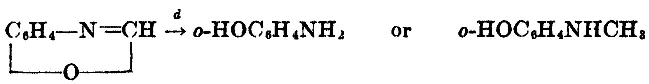
[a] Na in wet ether.[193]



[b] Na + alcohol.[194]



[c] Na + alcohol.[169]



[d] Na in liquid NH$_3$ or NH$_4$Br + Na in liquid NH$_3$, respectively.[195]

---

and Chivaler, *Monatsh.*, **28**, 270 (1907).

[190] Heller and Kühn, *Ber.*, **37**, 3112 (1904).

[191] Windaus, Dörries, and Jensen, *ibid.*, **54**, 2745 (1921).

[192] Oddo and Ingraffia, *Gazz. chim. ital.*, **62**, 1092 (1932)

[193] Claisen, *Ber.*, **24**, 3914 (1891).

[194] Fischer, *ibid.*, **29**, 205 (1896).

[195] Knowles and Watt, *J. Org. Chem.*, **7**, 56 (1942).

Acid reducing reagents sometimes cleave azoles. 2,4,5-Trimethylisoxazole[105] gives ammonia and a secondary alcohol when reduced by zinc and dilute sulfuric acid or by aluminum amalgam and dilute sulfuric–acetic acid. Diphenylfuroxan[196] gives an *amphi* dioxime. 2,5-Diphenyloxazole[4] is split by hydriodic acid at 200° into benzoic acid, ammonia, and other material.

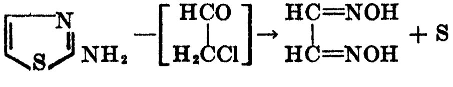
When pyrazoles are reduced to pyrazolines and these compounds, in turn, are heated, particularly in the presence of polished platinum, decomposition to cyclopropane[197] compounds results. The method is preparative for cyclopropanes.

Oxidative cleavage is not so common as other methods. Many rings are stable. The process converts side chains to carboxyl groups, which further stabilize the ring. When cleavage does take place, destruction of all primary compounds may occur.

An idea of the resistance that some azole rings have to break down during oxidation may be gathered from the fact that imidazole[167] is stable to chromic and nitric acid as might be expected from the acid medium. Pyrazole resists alkaline permanganate. When 1-phenyl-3-methyl-1,2,4 triazole[161] is treated with acid permanganate, the phenyl group is preferentially oxidized and removed; alkaline permanganate then oxidizes the methyl group. Although 2-methyl- or 2,4-dimethylthiazole[14] is completely destroyed by potassium chlorate and concentrated hydrochloric acid, the presence of a carbethoxy group in the 5-position prevents this oxidation.

Some azole systems can, however, be cleaved by oxidation fairly readily. Trimethyl- or triethyl-isoxazole[105] yields acetic or propionic acid, respectively. Imidazole, treated with hydrogen peroxide, gives an oxamide.[198] Although imidazole is stable to nitric or chromic acid, it is easily oxidized by alkaline permanganate.[167]

The presence of certain substituents on the nucleus will always make a ring more susceptible to ring opening. 2-Aminothiazole,[199] for example, is converted to a glyoxime and sulfur when heated with an aqueous solution of hydroxyl amine and hydrochloric acid.



Presumably, there is an initial hydrolysis to an α-chloroaldehyde (a reagent used in preparing the thiazole) which, after the general manner of α-chloroketones, reacts with hydroxylamine to give the dioxime.

---

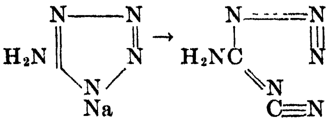
[196] Wieland, *Ann.*, **358,** 56 (1908).

[197] v. Auwers and König, *ibid.*, **496,** 252 (1932).

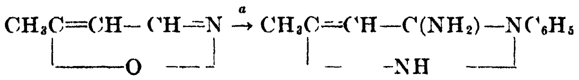
[198] Redzizewski, *Ber.*, **17,** 1289 (1884).

[199] Hantzsch and Wild, *Ann.*, **289,** 285 (1896).

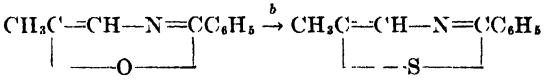
The sodium salt of 5-aminotetrazole, when treated with cyanogen bromide, forms a nitrile which, in turn, undergoes ring opening to a dicyanamidazide,[200] probably by way of an iminic compound.



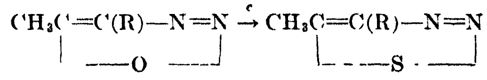
Replacement of the Oxygen Hetero Atom.—The oxygen atom in many azole systems can be replaced by nitrogen and sometimes by sulfur. The change is probably one of ring opening and re-formation. In the first example below, the ring has re-formed in such a way as to leave an amino substituent in the 3-position of a pyrazole system. Other examples have more the appearance of a simple replacement.



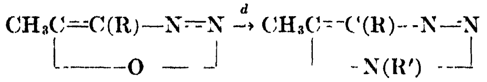
[a] Heated with $C_6H_5NHNH_2$.[104]



[b] Alcoholic H_2S at 280°.[169]



R = $-CO_2Et$ or $-C(O)CH_3$.
[c] H_2S or NH_4SH.[201]



R = $-CO_2Et$. R′ = H, OH, NHPh, $NHC(O)NH_2$.
[d] Treatment with NH_3, H_2NOH, $H_2NNHC_6H_5$, $H_2NNHC(O)NH_2$.[9,202]

REACTIVITY OF ATOMS OR GROUPS ATTACHED TO THE NUCLEUS

In general, substituents such as methyl-, chloro-, amino-, hydroxyl, carboxyl, and the like have properties expected in compounds that lean toward the pyridine type. For example, a *methyl group*, attached to the carbon of an ammono-aldehyde system, condenses with aldehydes in the presence of zinc chloride. Hence 2-methyl-4-phenyl-, but not 4-methyl-2-phenylthiazole, gives a styryl compound with benzaldehyde. The double bonds in these azoles may, accordingly, be regarded as more fixed than oscillating.[203] The greater reactivity of the 2-methyl group in

[200] Hart, *J. Am. Chem. Soc.*, **50**, 1922 (1928).

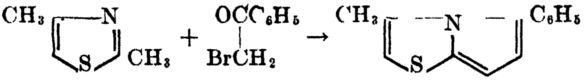
[201] Wolff, *Ann.*, **333**, 1 (1904).

[202] Wolff and Hall, *Ber.*, **36**, 3612 (1903).

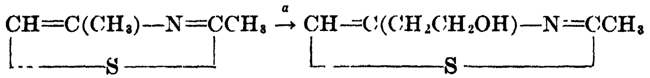
[203] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

2,4-dimethylthiazole toward benzaldehyde paves the way for conversion to a carboxyl group by ozonolysis and for eventual elimination by decarboxylation.[204]

Similarly, the hydrogen on the 2-methyl group of 2,4-dimethylthiazole is the one that reacts with bromoacetophenone. The product undergoes a subsequent intramolecular condensation that leads to a thiazolopyrrole.[170] This series of changes is identical with that by which α-picoline gives a pyridinopyrrole.[205]



An exception to this general rule of the most reactive methyl group occurs in the reaction of the 4-methyl rather than the 2-methyl group of 2,4-dimethylthiazole with 40 per cent formaldehyde in a sealed tube at 160°. The product is 2-methyl-4(β-oxyethyl)-thiazole.[180]

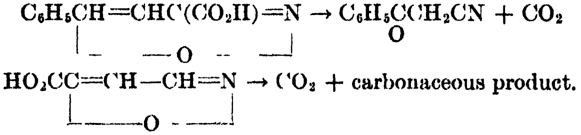


$$\underbrace{\text{CH}=\text{C(CH}_3)\text{—N}=\text{CCH}_3}_{\text{S}} \xrightarrow{a} \underbrace{\text{CH}=\text{C(CH}_2\text{CH}_2\text{OH)—N}=\text{CCH}_3}_{\text{S}}$$

[a] 40 per cent H_2CO at 160°.

Carboxyl groups, located at certain positions on an azole ring, have the lability that might be expected from the labilizing group in the ring. For example, 2-carboxy-1,3,4-triazole loses carbon dioxide at 137°.[161]

Isoxazolecarboxylic acids, as shown in the examples below, sometimes lose carbon dioxide and undergo ring cleavage when heated.[206] The



$$\underbrace{\text{C}_6\text{H}_5\text{CH}=\text{CHC(CO}_2\text{H)}=\text{N}}_{\text{O}} \rightarrow \text{C}_6\text{H}_5\underset{\text{O}}{\text{C}}\text{CH}_2\text{CN} + \text{CO}_2$$

$$\underbrace{\text{HO}_2\text{CC}=\text{CH—CH}=\text{N}}_{\text{O}} \rightarrow \text{CO}_2 + \text{carbonaceous product.}$$

formation of carbonaceous or pitchy products may be prevented sometimes by heating in the presence of phenylhydrazine, which will react with the ketone formed. The product, however, re-forms as an amino pyrazole. The yield of 5-amino-1,3-diphenylpyrazole[207] from 5-phenylisoxazole-3-carboxylic acid by this method is as high as 80 per cent.

Halogen atoms can be removed by reducing agents. 1-Methyl-2,4,5-tribromoimidazole[167] is converted to 1-methylimidazole by sodium

---

[204] KONDO and NAGASAWA, *J. Pharm. Soc. Japan*, **57**, 909 (1937); *C.A.*, **32**, 1699 (1938).

[205] CHITCHIBABIN, *Ber.*, **58**, 1704 (1925); **60**, 1607 (1927).

[206] QUILICO and FRERI, *Gazz. chim. ital.*, **59**, 930 (1929); *C.A.*, **24**, 3484 (1930).

[207] CUSMANO, *Gazz. chim. ital.*, **69**, 594 (1939); *C.A.*, **34**, 1319 (1940).

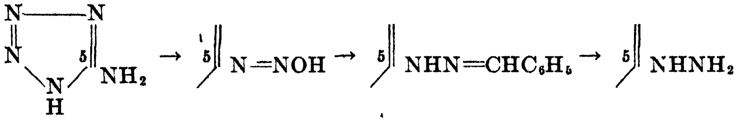
amalgam in warm alcohol solution; 1-methyl-5-chloroimidazole[208] is changed to the same compound by hydrogen iodide and phosphorus at 135 to 140°. Zinc dust and acetic acid eliminates the chloro- or bromo-group in 2-chloro- or bromo-thiazole.[169]

Halogen atoms sometimes show unexpected resistance to hydrolysis. 2-Chlorobenzothiazole[209] is unaffected by 10 hr. in boiling water. It does react, however, with liquid ammonia to give the 2-amino product. 2-Chlorobenzothiazole[122] is also not affected by heating with copper.

The activity of an *amino group* depends on the position occupied. If attached to the carbon of an ammono-aldehyde group, its behavior will approach that of α- and γ-aminopyridine, as shown by the conversion of 2-aminothiazole to thiazole,[210] to 2-bromothiazole,[169] or to 2-chlorothiazole[169] when treated with sodium nitrite and sulfuric, hydrobromic acid, or hydrochloric acid, respectively. The hydrochloride of the same amino compound, when treated with ethyl nitrite[107] or nitrous[211] acid in boiling alcohol, yields thiazole.

Although 2-aminobenzothiazole can be diazotized and the diazonium compound coupled with a solution of R salt, the process is slower than with aniline. The expected lower order of activity of the azole amino compounds is indicated by the fact that the 6-amino rather than the 2-amino group in 2,6-diaminobenzothiazole is diazotized.[212]

4-Amino-3,5-dimethylpyrazole and 5-amino-1,2,4-triazole can be diazotized. The sodium salt of 5-aminotetrazole forms an unstable diazo compound with sodium nitrite, which in concentrated solution explodes in a few seconds, but in boiling dilute solution decomposes smoothly. The diazotate condenses with benzaldehyde in the presence of zinc chloride and hydrochloric acid to give a benzaltetrazylhydrazine, which, in boiling 25 per cent hydrochloric acid, forms the tetrazylhydrazine.[178,213]



The amino group makes the azole more susceptible to substituting agents, very similar to the way it breaks down the resistance at the pyridine ring (see page 194). 2-Amino-4-methylthiazole[170] is nitrated or sulfonated in the 5-position. The sulfonation process can be halted

[208] Wallach and Schulze, *Ber.*, **14**, 422 (1881); Wallach, *Ann.*, **241**, 308 (1882).

[209] Lemons, Anderson, and Watt, *J. Am. Chem. Soc.*, **63**, 1953 (1941).

[210] Hertog and Wibaut, *Rec. trav. chim.*, **51**, 381, 940 (1932).

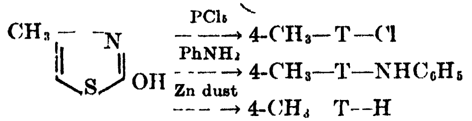
[211] Hantzsch and Popp, *Ber.*, **21**, 2582 (1888).

[212] Şkraup, *Ann.*, **419**, 1 (1919).

[213] Thiele and Marais, *ibid.*, **273**, 144 (1893).

at the intermediate sulfamino stage by using cold fuming sulfuric acid. Bromine also attacks the 5-position of the same compound.

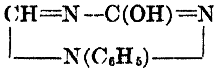
Hydroxy substituents lack a true phenolic character but nevertheless undergo many conventional reactions as shown below with 2-hydroxy-4-methylthiazole[214]

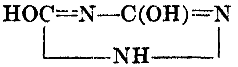


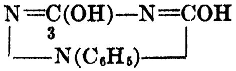
T = Thiazole nucleus.

The hydroxy group also labilizes the thiazole ring so that substitution takes place more readily. For example, the 2-hydroxy-4-methylthiazole mentioned above gives (*a*) the 5-sulfonic acid when treated with fuming sulfuric acid, (*b*) the 5-bromo product when treated with bromine in aqueous sulfuric acid, (*c*) the 2,5-dibromo compound when allowed to react with mercuric acetate and bromine in alcohol, (*d*) the 5-aldehydo compound when subjected to a Gattermann reaction with excess hydrogen cyanide, and (*e*) the 5-acetyl derivative when treated with acetic anhydride and aluminum chloride in nitrobenzene. A slight amount of substitution occurs also in a Reimer-Tiemann reaction.[170]

The hydroxy groups of some azoles are reduced by heating with phosphorus pentasulfide.[215,216] The hydroxyl group in 1-phenyl-3-hydroxy-1,2,4-triazole, urazol, and 1-phenylurazole, illustrated, respectively, below, are thus replaced by hydrogen. An intermediate mercaptan is probably formed. In the case of 1-phenylurazole, the 1-phenyl-3-mercapto-1,2,4-triazole can be isolated.


$\underset{\text{———}N(C_6H_5)\text{———}}{CH{=}N{-}C(OH){=}N}$


$\underset{\text{———}NH\text{———}}{HOC{=}N{-}C(OH){=}N}$


$\underset{\text{———}N(C_6H_5)\text{———}}{N{=}\underset{3}{C}(OH){-}N{=}COH}$

This reduction of the mercapto group is similar to that observed in the formation of thiophene compounds (page 40) in which the expected mercapto product is not found.

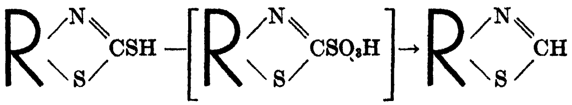
The *mercapto group* is a substituent in many thiazoles and imidazoles because of the formation of thio derivatives in the synthesis. It is oxidized readily by 10 per cent nitric acid to the sulfonic acid, which then undergoes hydrolysis spontaneously to give the thiazole or imidazole, respectively. The intermediate sulfonic acid can be isolated by

---

[214] Hantzsch and Weber, *Ber.*, **20**, 3118, 3336 (1887); Hantzsch and Arapides, *ibid.*, **21**, 941 (1888).

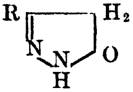
[215] Pellizzari and Ferro, *Gazz. chim. ital.*, **28**, II, 541 (1898); Andreocci and Mannino, *ibid.*, **29**, II, 41 (1899).

[216] Thiele and Uhlfelder, *Ann.*, **303**, 94, 102 (1898); Diels, *Ber.*, **36**, 739 (1903); Stollé and Krauch, *J. prakt. Chem.* [2], **88**, 313 (1913).

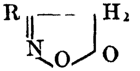


oxidation with hydrogen peroxide and potassium hydroxide.

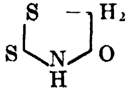
Reactions of Azolones.—The reactivity of azolones is, to a large extent, a problem of an active methylene group adjacent to the carbonyl and often also to the —C═N— system in the ring. Reactions are typical of like systems in the malonic, dimethyldihydroresorcinol, and other systems. For example, the four different types of pyrazolones[217] shown below react easily with nitrous acid, the nitrosites of tertiary bases, aldehydes, diazonium salts, isatin chloride, etc.



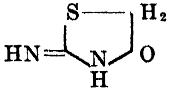
Pyrazolone-5



Isoxazolone

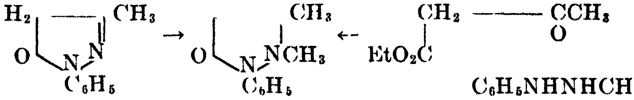


Rhodanic acid



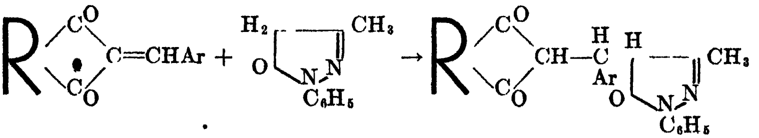
Thiohydantoin

The hydrogen atom in 1-phenyl-3-methylpyrazolone-5 undergoes tautomerism so that the N-methyl derivative is obtained with potassium hydroxide and methyl iodide or with sodium hydroxide and dimethylsulfate. The structure of this product is proved by its independent



synthesis from ethyl acetoacetate and *sym*-methyl phenyl hydrazine.

The same pyrazolone can add across double bonds as indicated in the formation of the carboindogenide[218] (see page 311).



Ar means phenyl, *m*- or *p*-chlorophenyl, *p*-tolyl, or -*p*-acetoxyphenyl but not aromatic systems with a methoxy, hydroxy, or dimethylamino group.

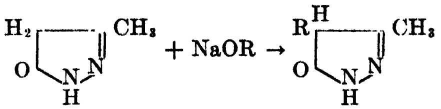
3-Methylpyrazolone-5 undergoes an interesting reaction[219] with sodium alkoxides which is reminiscent of some that occur with pyrrole (page 63). When heated, at 210 to 230° for 8 to 22 hr., an alkyl group is introduced in the 4-position. Methyl, ethyl, propyl derivatives are thus

---

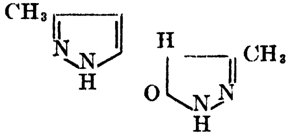
[217] Wahl and Bagard, *Bull. soc. chim.* [4], **5**, 1033 (1909).

[218] Ionescu and Georgescu, *Bull. soc. chim.*, **45**, 428 (1929).

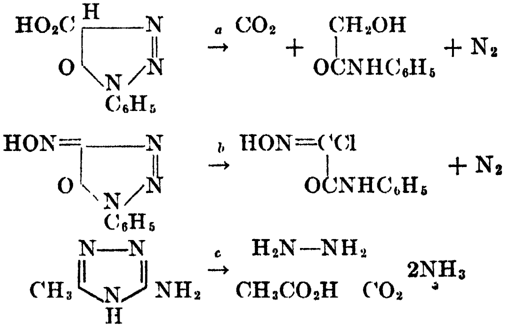
[219] Wolff and Thielepape, *Ann.*, **420**, 275 (1920).



obtained. A second alkyl group is not introduced into 3,4-dimethylpyrazolone. If the sodium propoxide used is not dry, the condensation takes another course that gives a pyrazylpyrazolone (m.p. 259°)

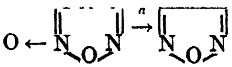


Obviously, azolones are more susceptible than azoles to hydrolytic scission. Triazolones or amino compounds capable of forming triazolones are sometimes hydrolyzed by water or aqueous acid. Stronger conditions may be employed as necessary. A few examples are shown below.



[a] H_2O.[220] [b] Fuming HCl.[221] [c] Dilute H_2SO_4 at 180°.[222]

Furoxans may be regarded superficially as related to the azolones in that they are N-oxides rather than C-oxides. Chemically, there are only a very few points of similarity. Furoxans[28] have an interesting number of reactions. Reducing agents, such as hydriodic acid or tin and hydrochloric acid, or phosphorus pentachloride, eliminate oxygen



[a] HI or Sn + HCl give furazan and water. PCl_5 gives the furazan, phosphorus oxychloride and chlorine.

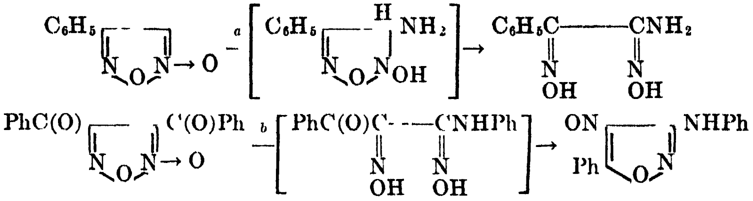
---

[220] Dimroth, *ibid.*, **325**, 90 (1904); **364**, 195 (1909).

[221] Dimroth and Taub, *Ber.*, **39**, 3912 (1907).

[222] Thiele and Heidenreich, *ibid.*, **28**, 2598 (1893) Thiele and Manchot, *Ann.*, **303**, 39 (1898).

and give the furazan. Ammonia and aniline add 1,3- (see page 198) and form dioximes as the primary products.



Ph = C_6H_5.
[a] NH_3. [b] $C_6H_5NH_2$.

The aniline product undergoes enolization and further condensation to a nitroso isoxazole, according to the general manner given before (page 364) for obtaining isoxazoles from molecules that have appropriately placed oxime and benzoyl groups.

CHAPTER XIV

AZOLES

PART II. COMPOUNDS

The number of known azoles is far too numerous to permit[1] a detailed account of each. The parent compounds and their methyl homologues have already been mentioned in the general discussion and tables of the previous chapter; and this reference is adequate because they are far less important than their analogues in the benzene and pyridine series, which are obtained in commercial quantities and form the basis for a large field of chemistry. The major discussion in this chapter will be

TABLE I.—SOME OXAZOLES AND REAGENTS USED IN THEIR PREPARATION

Substituent	M.p., °C.	B.p., °C.	Preparation	Ref.
2,4-Dimethyl	liquid	108	a	2
2,5-Dimethyl	liquid	118	b	3
2-Methyl-5-phenyl	59	256/748	c	3
5-Methyl-2-phenyl	Oil	255/734	d	3
2,4-Dimethyl-5-phenyl	52	....	e	4
5-Phenyl	42	....	f	4
4-Phenyl	6	....	g	5
2,4-Diphenyl	103.5	....	h	5
2,5-Diphenyl	74	....	i	6
4,5-Diphenyl	44	....	j	7
2,4,5-Triphenyl	116	....	k	7,8

[a] Chloroacetone and acetamide. [b] Acylation and dehydration of aminoacetone. [c] Acetaminoacetophenone and phosphorus pentachloride. [d] Benzoylaminoacetone and phosphorus pentachloride. [e] Acetoaminopropiophenone and phosphorus pentachloride. [f] Formaminoacetophenone and phosphorus pentasulfide. [g] ω-Bromoacetophenone and formamide. [h] ω-Bromoacetopheone and benzamide [i] Benzaldehydecyanohydrin and benzaldehyde. [j] Benzoin, hydrogen cyanide, and sulfuric acid. [k] Benzoin, ammonia, and benzoyl chloride, followed by concentrated sulfuric acid.

---

[1] In order to simplify the writing of formulas, the capital letters O, Is, T, P, and I will be used frequently to designate the oxazole, isothiazole, thiazole, pyrazole, and imidazole nucleus. The context will supply enough information so that no confusion as to the meaning will exist. In the case of aromatic nuclei, the large letter R will be used frequently to designate the system attached to the heterocyclic atoms.

[2] SCHUFTAN, *Ber.*, **28**, 3070 (1895); ÖSTERREICH, *ibid.*, **30**, 2254 (1897).

[3] GABRIEL, *ibid.*, **43**, 1283 (1900).

[4] BACHSTEZ, *ibid.*, **47**, 3163 (1914).

[5] HANTZSCH, *ibid.*, **21**, 942 (1888); LEWY, *ibid.*, **20**, 2576 (1887).

[6] ROBINSON, *J. Chem. Soc.*, **95**, 2169 (1909); GABRIEL, *Ber.*, **43**, 136 (1910).

[7] JAPP and MURRAY, *J. Chem. Soc.*, **63**, 469 (1893).

[8] MCKENZIE and BARROW, *ibid.*, **103**, 1331 (1913).

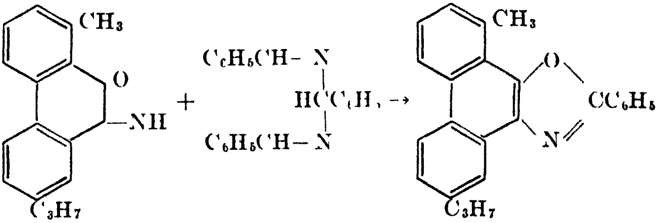
devoted to compounds of some theoretical, commercial, medical, or novel interest. There are relatively few such compounds among the oxazoles and isoxazoles, perhaps because of their sensitivity to hydrolysis; there are many among the thiazoles, pyrazoles, and imidazoles; and there are few again among the oxadiazoles, thiadiazoles, triazoles, and tetrazoles.

OXAZOLES

Some oxazoles and the methods used in their preparation are recorded in Table I, in order to emphasize the reagents used in their formation.

Oxazolines may be regarded as derivatives of N-acyl-2-aminoethanols. They should, therefore, have some physiological interest. The compounds can be prepared from 2-aminoethanol by acylation (heating with an acid to 200°) and then dehydration of the N-acylated or benzoylated amino ethanol by heat or phosphorus pentoxide. 2-Methyl-, 2-ethyl-, and 2-phenyl-oxazoline boil at 111, 125, 248°, respectively.[9] Treatment of the same intermediate with phosphorus pentasulfide gives also the corresponding thiazoline.

Phenanthraquinone,[10] or retenequinone,[11] forms an oxazole, together with some imidazole, when dissolved with an aromatic aldehyde in boiling absolute alcohol or toluene that is saturated with a rapid stream of ammonia. The reaction probably progresses[11] through the intermediate quinonimine and hydrobenzamide derivatives as illustrated in the case of retenequinonimine below.



Retenequinonimine, with *n*-butylamine or piperidine as a catalyst, forms a 2-phenylphenanthroxazole with benzaldehyde and a 2-propylphenanthroxazole with *n*-butyraldehyde[12] as if by an intermediate aldol condensation. *2-Phenylphenanthroxazole* melts at 204 to 205.5°; *2-phenylreteneoxazole* melts at 174.5 to 176°.

2-Methyl-α-naphthoxazole[13] is prepared by a conventional sequence of reactions from α-naphthol as shown below.

---

[9] Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

[10] Japp and Wilcock, *J. Chem. Soc.*, **37**, 661 (1880); **39**, 225 (1881); Sircar and Sircar, *ibid.*, **123**, 1559 (1923).

[11] Kreps and Day, *J. Org. Chem.*, **6**, 140 (1941).

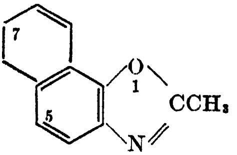
[12] Stein and Day, *J. Am. Chem. Soc.*, **64**, 2567 (1942).

[13] Fisher and Hamer, *J. Chem. Soc.*, 962 (1934).

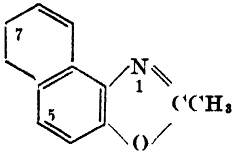
α-naphthol $\xrightarrow{a}$ 2-nitroso-α-naphthol $\xrightarrow{b}$ 2-nitro-α-naphthol $\xrightarrow{c}$ 2-amino-α-naphthol $\xrightarrow{d}$ 2-methyl-α-naphthoxazole

[a] NaOH + HNO_2. Some of the 4-nitroso isomer is obtained also. [b] H_2O_2 + $FeSO_4$ + NaOH. [c] Sn + HCl. [d] Ac_2O + NaOAc.

The β-isomer is obtained similarly from β-naphthol.

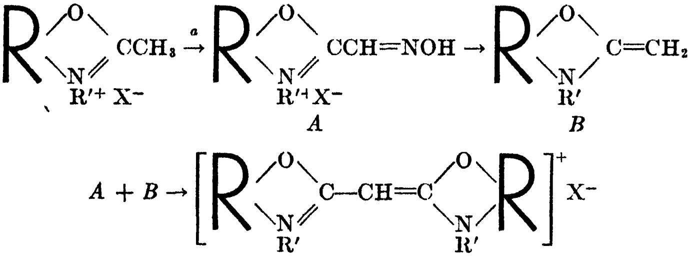


2-Methyl-α-naphthoxazole
M.p. 36 to 37°
Methiodide, m.p. 202 (d.)



2-Methyl-β-naphthoxazole
M.p. 27°
Methiodide, m.p. 212 to 213 (d.)

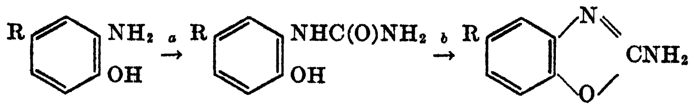
Oxacyanines.—The absorption of the oxacyanines lies further in the more refrangible region of the spectrum than that of any known kind of cyanine dye.[13] The general method of preparation[13,14] involves formation of an oxime *A* at an active methyl group, decomposition of the oxime to *B*, and condensation of *A* with *B* to form the dye. The intermediate products are not isolated during the process.



R = C_6H_4 or $C_{10}H_6$; R' = CH_3 or C_2H_5.
[a] $C_5H_{11}ONO$.

The simplest oxacyanines cause a negligible photographic shift; the dibenzoxacyanines, however, are powerful sensitizers for gelatin chloride emulsions.

1-Aminobenzoxazole-4-arsenic acid has been prepared by a conventional process, as shown below, because of its possible physiological interest as an arsenic containing compound.[15]



R = NaOAs(O)OH.
[a] BrCN and water. Amines react with cyanogen bromide to form a cyanamide and then a guanidine derivative which undergoes hydrolysis to a urea compound. [b] Strong alkali.

---

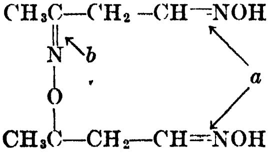
[14] Kuhn, Winterstein, and Balser, *Ber.*, **63**, 3176 (1930).
[15] Stickings, *J. Chem. Soc.*, 3131 (1928).

Azlactones are 2-phenyl-4-benzal-5-oxazolones or similar compounds, obtained[16] by condensation of aldehydes with hippuric acid under the influence of acetic anhydride. They are valuable as intermediates in the synthesis of α-amino acids such as tryptophan. The reaction is general.[17]

ISOXAZOLES

No naturally occurring isoxazole compounds are known. They are often obtained in the course of laboratory work with nitroso and isonitroso compounds. The first known compound, a 3-phenyl-5-methylisoxazole,[18] came from an attempt to prepare an oxime from benzoylacetone. Subsequently, acetylacetone[19] was shown to undergo a similar condensation and form 3,5-dimethylisoxazole.

3- and 5-Methylisoxazoles.—The preparation of these compounds from sodioacetaldehyde proceeds by way of an intermediate product, $C_8H_{13}O_3N_3$, formed by interaction with hydroxyl amine.[20] Treatment of this intermediate with $n/2$ hydrochloric acid gives 5-methylisoxazole, and with more concentrated acid it gives the 3-methyl isomer. A conversion does not occur after the 5-methyl product is formed. A possible formula of the sesquioxime intermediate is pictured below. If hydrolysis at (*a*) precedes that at (*b*), the only isoxazole possible is the 3-isomer. Otherwise the 5-methylisoxazole results.



Isoxazolecarboxylic Acids.—Table II lists the properties of a number of these compounds.

Isoxazole-5-azotrinitromethane, $C_3H_2NO{\cdot}N{=}NC(NO_2)_3$.—When acetylene is bubbled through fuming nitric acid, a mixture, consisting principally of isoxazole-5-carboxylic acid, α,β′-diisoxazoyl ketone, $C_7H_4O_3N_2$, and a yellow explosive compound, $C_4H_2O_7N_6$, is obtained.[22] The last product, the azotrinitromethane, is insoluble in alkali and gives a red color with unsaturated compounds, as does trinitromethane. Stannous chloride reduces it to $C_4H_7O_3N_5{\cdot}HCl$. It is synthesized[21] from isoxazole azide by reduction ($SnCl_2$) to the amine, treatment with nitrous acid to form the azo compound, $C_3H_2NO{\cdot}N{=}NOH$, and condensation of this product with trinitromethane. The melting point, when heated cautiously, is 78°. It explodes when heated rapidly or struck. A related compound, $C_6H_5N{=}N{-}C(NO_2)_3$, in the aromatic series behaves similarly.

---

[16] Erlenmeyer *et al.*, *Ann.*, **275**, 3 (1893); **337**, 266 (1904).

[17] Raiford and Buurman, *J. Org. Chem.*, **8**, 466 (1943).

[18] Claisen and Lowman, *Ber.*, **21**, 1149 (1888).

[19] Zedel, *ibid.*, **21**, 2178 (1888).

[20] Bell, *J. Chem. Soc.*, 285 (1941).

[21] Freri, *Gazz. chim. ital.*, **62**, 457 (1932); *C.A.*, **26**, 5952 (1932); Quilico, *Gazz. chim. ital.*, **62**, 503 (1932); *C.A.*, **26**, 5953 (1932).

TABLE II.—PROPERTIES OF SOME ISOXAZOLE CARBOXYLIC ACIDS

Isoxazole carboxylic acid		M.p., °C.	Ester*	M.P., °C.	Prep.	Ref.
Substituent	Position of carboxyl group					
None	5	149	E	1	*a*	22
5-Methyl-	3	170 d.	M	94	*b*	23
3-Methyl-	5	211	E	1	*c*	24
5-Phenyl-	3	162	E	52	*d*	25
3-Methyl-5-phenyl	4	189	E	50	*e*	26
5-Keto	4		E	185 d.	*f*	27

* ε = ethyl, M = methyl.

[a] From acetylene and nitric acid.

[b] From oxaloacetone and hydroxylamine hydrochloride.

[c] From ethyloxaloacetone and hydroxylamine hydrochloride.

[d] From ethyl benzoylpyruvate and hydroxylamine.

[e] From ethyl β-methylamino-α-benzoylcrotonate or ethyl benzoylacetoacetate.

[f] From ethyl ethoxymethylenemalonate and hydroxylamine.

[22] QUILICO and FRERI, *Gazz. chim. ital.*, **59**, 930 (1929); *C.A.*, **24**, 3484 (1930).

[23] MUMM and BERGELL, *Ber.*, **45**, 3040 (1912).

[24] CLAISEN, *ibid.*, **42**, 60 (1907).

[25] ANGELI, *ibid.*, **23**, 2159 (1888).

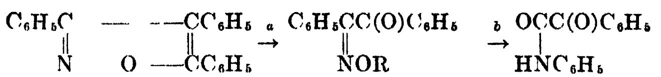
[26] BENARY, *ibid.*, **42**, 3912 (1909); BETTI and BERLINGOZZI, *Gazz. chim. ital.*, **51**, II 230 (1921).

[27] CLAISEN and HAASE, *Ber.*, **30**, 1480 (1897); *Ann.*, **297**, 81 (1897).

Triphenylisoxazole and the Beckmann Rearrangement.—*Triphenylisoxazole* is prepared from nitrostilbene and benzaldehyde or from benzaldehyde and phenylnitromethane with methylamine as a condensing agent (see page 377). It melts at 212 to 213°. A study of this compound furnished the first evidence[28] on the trans mechanism of the Beckmann rearrangement. The positions of all atoms in the ring are, of course, fixed. Hence, the configuration of the benzoylated oxime, prepared by ozonization of the isoxazole, is fixed. Since the structure of the oxime is thus established, and the oxime is the starting point of the Beckmann rearrangement, the final product can come only from a trans interchange. Prior to this study, the rearrangement had been assumed to take place between groups that were on the same side, *i.e.*, by a cis change.

---

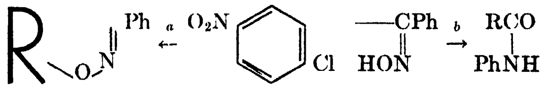
[28] MEISENHEIMER, *Ann.*, **446**, 205 (1926); *Ber.*, **54**, 3195, 3206 (1921); BLATT, *Chem. Rev.*, **12**, 215 (1933).



[a] Proof of configuration of oxime by ozonization of the isoxazole. R = $C(O)C_6H_5$ in the product
[b] Beckmann rearrangement of the oxime (R=H) under the influence of PCl_5.

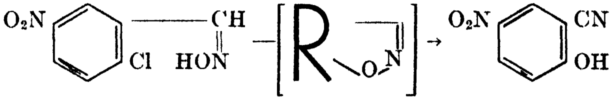
Ozonization of 3,4-diphenyl-5-*p*-bromophenylisoxazole[29] and 3,5-diphenyl-4-anisylisoxazole[30] likewise establish configuration of the oxime and confirm the idea of a trans shift.

Synthesis of isoxazoles gives another clue to the configuration of oximes and the course of the Beckmann change. A single oxime each is obtained from 2-chloro-,[31] 2-bromo-,[31] 2-chloro-5-nitro-,[32] or 2-bromo-5-nitrobenzophenone;[32] and each oxime undergoes ring closure (forms an indoxazene) and gives Beckmann rearrangement products in accordance with a trans mechanism. *o*-Aminobenzophenone oxime exists in two forms, only one of which, by diazotization, gives a benzisoxazole; and this same oxime gives the anilide of anthranilic acid by a trans change.



Large R = $NO_2C_6H_3$. Small R = $NO_2(Cl)C_6H_3$.
[a] Ring closure. [b] Beckmann rearrangement.

2-*Chloro-5-nitrobenzaldoxime*[33] should form an isoxazole if the configuration of the oxime is suitable, though the isoxazole is unstable and undergoes ring opening in the presence of the alkali reagent. Nevertheless the facility of ring closure is reflected by a 53 per cent yield of ionizable halogen in 4 hr. from the syn-form of the oxime as compared with none from the anti-form. The Beckmann rearrangement products from these two oximes must be by a trans mechanism to agree with the structure deduced for the oximes from these facts.

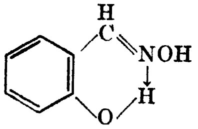


Large R = $O_2NC_6H_3$.

The configuration for aldoximes can be judged also from coordination formulas.[34] Salicylaldoxime, for example, is sparingly soluble in water, is very soluble in organic solvents, and is more volatile than expected. It probably has the chelated structure, which has some of the appearances of a heterocyclic ring system. The other oxime form of salicylaldoxime is unknown. Dipole moments[35] of the N-ethers of *p*-nitro-

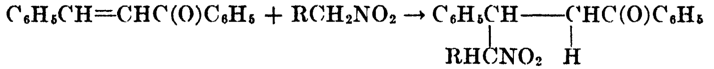
---

[29] Kohler and Richtmyer, *J. Am. Chem. Soc.*, **50**, 3903 (1928).
[30] Meisenheimer and Lange, *Ber.*, **57**, 282 (1924).
[31] Meisenheimer and Meis, *ibid.*, **57**, 289 (1924).
[32] Meisenheimer, Zimmermann, and Kummer, *Ann.*, **446**, 205 (1926).
[33] Brady and Bishop, *J. Chem. Soc.*, **127**, 1357 (1925).
[34] Brady, *ibid.*, 105 (1931).



phenone oxime also accord with a trans mechanism.

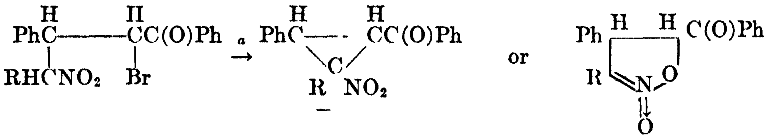
Isoxazoline Oxides.—Nitromethane or phenylnitromethane saturates the carbon-carbon double bond of benzalacetophenone and forms two



$$C_6H_5CH{=}CHC(O)C_6H_5 + RCH_2NO_2 \rightarrow \underset{RHCNO_2}{C_6H_5CH}\text{——}\underset{H}{CHC(O)C_6H_5}$$

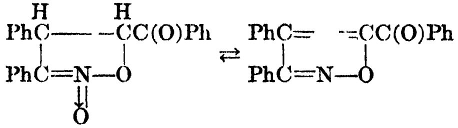
R = H or C_6H_5.

stereoisomeric γ-nitro ketones. Bromination yields two bromo derivatives for each ketone, from which elimination of hydrogen bromide gives a nitrocyclopropane (when nitromethane is used) or isoxazoline oxide.[36]



ᵃ KOAc in CH_3OH.

From the four isomeric α-bromo compounds, two stereoisomeric isoxazoline oxides are obtained. The oxides lose water readily with concentrated aqueous ammonia, acetyl chloride, or phosphorus pentachloride and form the isoxazole; hydrogen peroxide re-forms the oxide.



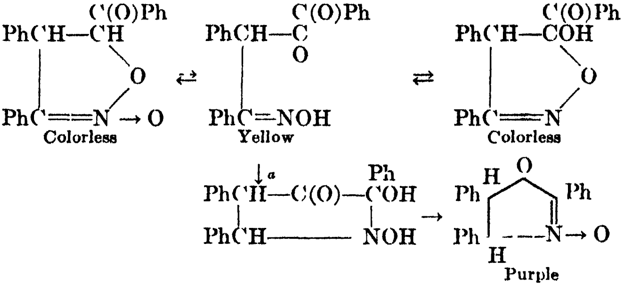
3,4-Diphenyl-5-benzoylisoxazole is insensitive to acids, bases, and oxidizing agents. It behaves as an aromatic ketone in that it forms an oxime, a tertiary alcohol with the Grignard reagent, and a secondary alcohol with zinc dust and acetic acid. Chromic-acetic acid reconverts the ketone from the secondary alcohol.

In ether or alcohol solution, the colorless isoxazole exists in equilibrium with the yellow nonheterocyclic triketone oxime, which in turn is in equilibrium with another colorless isoxazoline compound. In chloroform

---

[35] SUTTON and TAYLOR, *ibid.*, 2190 (1931).

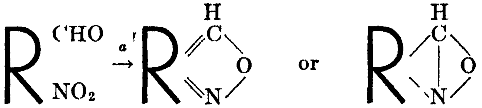
[36] KOHLER, *J. Am. Chem. Soc.*, **46**, 503, 1733 (1924); **50**, 221 (1928); KOHLER and BLATT, *ibid.*, **50**, 1217 (1928); KOHLER and RICHTMYER, *ibid.*, **50**, 3092 (1928); **52**, 2038 (1930).



[a] Trace of acid in chloroform.

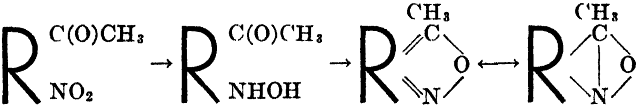
solution with a trace of acid, a deep purple nitrone forms, presumably by way of the yellow triketone oxime. The nitrones have properties similar to those of the isatogens (page 139).

Anthranils.—Anthranil or 2,1-benzisoxazole[37] is obtained by reduction of *o*-nitrobenzaldehyde by tin and acetic acid. The name is derived



[a] Sn + HCl.

from the fact that warm alkali converts it to anthranilic acid, as if the compound were a lactam. The compound is regarded as a benzisoxazole rather than a lactam because reduction of *o*-nitroacetophenone, which cannot form a lactam, gives the methyl homologue of anthranil.[38] The reduction proceeds by way of the intermediate hydroxyamino compound.



Anthranil is a colorless liquid ($D_4^{20} = 1.183$) that boils at 210 to 215°. The mercuric chloride addition compound melts at 178.5°. Like the other isoxazoles, it is easily cleaved. Ferrous sulfate and ammonia reduce it quantitatively to *o*-aminobenzaldehyde.[39] Acid permanganate (3 per cent) converts is to 2-nitrosobenzaldehyde,[40] and excess permanganate oxidizes it to 2-nitrobenzaldehyde.[40] Hydroxylamine opens the ring and yields the oxime of hydroxylaminobenzaldehyde, *o*-$HONHC_6H_4$-

---

[37] Friedländer and Henriques, *Ber.*, **15**, 2605 (1882).

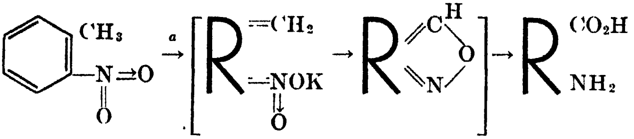
[38] Bamberger, *ibid.*, **36**, 819, 839 (1903); **48**, 537 (1915); *J. prakt. Chem.* [2], **81** 254 (1910).

[39] Friedländer, *Ber.*, **15**, 2572 (1882).

[40] Bamberger and Fodor, *ibid.*, **45**, 3333 (1912).

CH=NOH. Anthranil is stable to acids but suffers conversion to anthranilic acid with alkali.

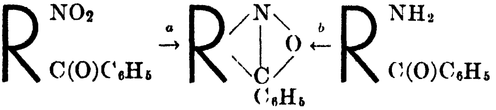
An anthranil may well be an intermediate[41] in the formation of anthranilic acid from *o*-nitrotoluene and hot 70 per cent potassium hydroxide. The exact mechanism is unknown, but the following steps are rational:



[a] 1,4-Addition of KOH followed by elimination of water and then of KOH to give the anthranil which undergoes hydrolysis to anthranilic acid.

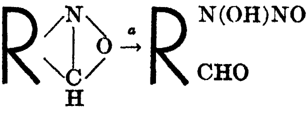
Formation of traces of indigo by distillation of *o*-nitroacetophenone with zinc and soda lime may take place by way of an intermediate methyl anthranil,[42] which then rearranges to indoxyl.

Substituted anthranils may be obtained by the reduction method or by oxidation of the corresponding amino compound,[43a] as shown below.



[a] Sn in CH_3CO_2H. [b] Permonosulfuric acid.

Anthranils undergo diazotization in strong sulfuric acid and $NaNO_2$ and couple with β-naphthol.[43b] Diazotization of 3-phenylanthranil yields acridone (see section on Acridone). Formation of diazonium salts in mineral acids proceeds through the formation of an intermediate nitrosophenylhydroxylamine.[44]



[a] HNO_2 in 23 per cent HCl at −17°.

Evidences for the structure of this inital product are (*a*) the acidic character; (*b*) the formation of an inner ferrous iron complex which is like that from nitrosophenylhydroxylamine, in that it is soluble in ether and precipitates no sulfide from an acetone-acetic acid solution containing hydrogen sulfide; (*c*) the formation of a phenylhydrazone which is acidic and forms a ferro complex; (*d*) the formation of a diazonium salt with acids; and (*e*) a conversion to an azoxybenzaldehyde. The steps to the diazonium salt are represented by a series of equations analogous to the behavior of nitrosophenylhydroxylamine.

---

[41] Scholl, *Monatsh.*, **34**, 1011 (1913); Lock, *Ber.*, **73**, 1377 (1940).

[42] Bamberger and Elgar, *ibid.*, **36**, 1611 (1903).

[43a] Bamberger, *ibid.*, **42**, 1707 (1909).

[43b] Bamberger and Lindberg, *Ber.*, **42**, 1723 (1909).

[44] Bamberger and Lublin, *ibid.*, **42**, 1676 (1909).

$$2RN(OH)NO + 2HCl \rightarrow RN_2Cl + RNO + HNO_2 + H_2O$$

$R = OHCC_6H_4-.$

The nitrous acid formed in this step reacts with more nitrosohydroxylamine as follows:

$$RN(OH)NO + HNO_2 \rightarrow RN_2NO_3 + H_{20}$$

The over-all equation is:

$$3RN(OH)NO + HCl \rightarrow RN_2Cl + RN_2NO_3 + RNO + 2H_2O$$

THIAZOLES

Thiazoles are found in nature and are readily prepared in the laboratory by methods outlined in the previous chapter. Many compounds have attained commercial importance.

2-*Aminothiazole* (m.p. 90°) is an intermediate in the preparation of sulfathiazole. It is obtained by boiling an aqueous suspension of thiourea and α,β-dichloroethyl ether,[45] the latter reagent being one that furnishes chloroacetaldehyde *in situ*. Diazotization[46] of the compound by alkali or alkyl nitrites in hydrochloric or hydrobromic acids gives unstable diazonium salts that decompose and yield 2-chloro- or 2-bromo-thiazole.

Sulfathiazole is one of the important members of the series of sulfa drugs.[47] It is prepared from 2-aminothiazole by reaction with *p*-aminobenzenesulfonyl chloride.[48] It melts at 202 to 202.5° (corr.) and dissolves slightly in water. The sodium salt melts at 264.5 to 265° (corr.).

The theory of its action, and also of other members of the sulfa series, is that bacteria absorb *p*-aminobenzoic acid for growth and reproduction, but that their absorption apparatus cannot differentiate between the acid and a sulfonamide. The latter will not, however, substitute in the enzymatic process leading to multiplication. Hence the bacteria do not multiply and the normal reagents in the body can destroy the comparatively small number present. The most active sulfa agent is, therefore, the one most similar in molecular structure and electric-charge distribution to the *p*-aminobenzoate ion. The activity of the sulfanilamides is, indeed, shown to be related to the acid dissociation constant of the amide.[49]

---

[45] TRAUMANN, *Ann.*, **249**, 35 (1888).

[46] MORGAN and MORROW, *J. Chem. Soc.*, **107**, 1293 (1915).

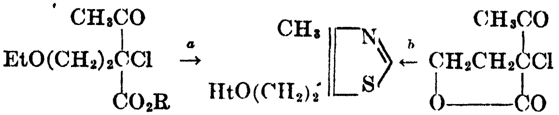
[47] NORTHEY, *Chem. Rev.*, **27**, 85 (1940); *Ind. Eng. Chem.*, **35**, 829 (1943).

[48] FOSBINDER and WALTER, *J. Am. Chem. Soc.*, **61**, 2032 (1939); LOTT and BERGUM, *ibid.*, 3593.

Sulfasuxidine is the N-succinyl derivative of sulfathiazole, $HOOCCH_2CH_2C(O)NHC_6H_4SO_2NHC_3H_2NS$.

4-Methyl-5-(β-hydroxyethyl)-thiazole, C_6H_9NSO, is the thiazole half of thiamine chloride (vitamin B_1, see page 486). It boils at 93 to 95°/2 mm. and is a hygroscopic crystalline material, the picrate of which melts at 162°. It is obtained from the vitamin by sulfite cleavage.[50] The presence of a thiazole nucleus is demonstrated by characteristic absorption spectra, resistance to alkaline plumbite, and oxidation with bromine water to sulfuric acid. An alcoholic function is present. Oxidation with nitric acid gives 4-methylthiazole-5-carboxylic acid.

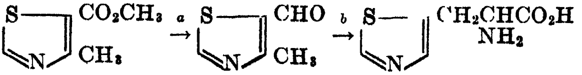
Two methods of synthesis from ethyl acetoacetate[51,52] are shown below.



[a] The starting material is prepared from ethyl acetoacetate, sodium ethoxide, and β-bromoethyl ether followed by thionyl chloride. Subsequent treatments are with thiourea followed by conversion of the ether to a chloride by HCl at 150° and hydrolysis of the chloride with water at 150°.

[b] The starting material is prepared from ethyl acetoacetate, sodium ethoxide, and ethylene oxide, followed by thionyl chloride. Subsequent treatments are with concentrated HCl to hydrolyze the lactone and simultaneously eliminate the carboxyl group, and with thiourea to form the thiazole ring.

β-(4-Methylthiazolyl-5-)-alanine.—This compound[53a] may be a precursor of the thiazole half of thiamine, if a compound of the tryptophan type is assumed to be present in nature. The steps in the synthesis include a novel formation of an aldehyde by decomposition of the benzenesulfonyl derivative of the hydrazide and the conventional synthesis of an α-amino acid by way of the azlactone.



[a] The starting compound is prepared from methyl acetoacetate and thionyl chloride followed by reaction with thioformamide. A sequence of treatments with H_2NNH_2, $C_6H_5SO_2Cl$, and Na_2CO_3 converts it to the aldehyde. Method of McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

[b] Conversion to the amino acid by the azlactone synthesis.

Penicillin.—This compound, produced by a mold, is a thiazolidin that has either the lactone or an incipient azlactone structure,[53b] shown respectively as the sodium salts, below.

---

[49] Bell and Roblin, *ibid.*, **64**, 2905 (1942); see, however, Henry, *Bact. Revs.*, 7175 (1943).

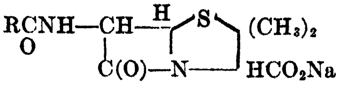
[50] Williams, Waterman, Keresztesy, and Buchman, *J. Am. Chem. Soc.*, **57**, 536 (1935).

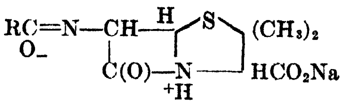
[51] Clarke and Gurin, *ibid.*, **57**, 1876 (1935).

[52] Buchman, *ibid.*, **58**, 1803 (1936).

[53a] Buchman and Richardson, *ibid.*, **61**, 891 (1939).

[53b] Committee on Medical Research, O.S.R.D., *Science*, **120**, 627 (1945).

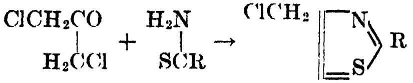




The R may be a Δ^2-pentenyl, *n*-amyl, *n*-heptyl, benzyl, or a *p*-hydroxybenzyl radical depending on the source of the compound.

Hydrolytic cleavage of the amide system forms a dicarboxylic acid, penicilloic acid, that has an unstable carboxyl group. Hot dilute mineral acid liberates carbon dioxide and gives penaldic acid, penicillamine, which is *d*-β,β-dimethylcysteine, and an aldehyde that comes from the decarboxylation of penaldic acid, $RC(O)NHCH(CO_2H)CHO$. When the ring is opened by methanol cleavage, the methyl ester of the acid is obtained. Benzylamine gives a monobenzylamine salt of the monobenzyl amide of a dicarboxylic acid, and this compound in turn is degraded by mercuric chloride to penicillamine and the benzylamide of penaldic acid benzylamide. Catalytic hydrogenation of this last compound gives $RC(O)NHCH(CH_2OH)C(O)NHC_7H_{13}$.

Thiazolyl Chlorides and Related Compounds.—Chlorides, comparable to benzyl chloride, are made by condensation of dichloroacetone[54] with thioamides.



R = alkyl, phenyl, anisyl.

The 2-alkyl compounds of this type polymerize[55] spontaneously to a solid which is probably a piperazine. The halogen reacts[56] with ammonia, potassium phthalimide, diethyl sodiomalonate, and like reagents. Ethyl 2-phenylthiazole-4-β-propionate, derived from a chloride of the above type, forms the starting point for conversion to an ethyl amine by a series of reactions that are general for preparing the physiologically active β-substituted ethyl amines.

$$RTCH_2Cl \xrightarrow{a} RTCH_2CH_2CO_2H \xrightarrow{b} RT(CH_2)_2NHC(O)NH_2 \xrightarrow{c} RT(CH_2)_2NH_2$$

R = C_6H_5; T = thiazole nucleus.

[a] Reaction with NaCH $(CO_2Et)_2$ followed by saponification and partial decarboxylation.

[b] Conversion to the urea compound by way of the ester, hydrazide, azide, and heat.

[c] Hydrolysis by means of phthalic anhydride followed by hydrolysis of the phthalimide.

Rhodanine, 2-mercaptothiazolidone-4, is conveniently obtained[57] from ammonium dithiocarbamate ($CS_2 + NH_3$) and sodium chloroacetate, or less readily from thioglycolic acid and thiocyanic acid. The pale yellow crystals melt at 168 to 170° and dissolve in hot water, alcohol, or ether. The acidity (K_A at 25° = 3×10^{-6}) is sufficient to permit titration by alkali with phenophthalein as an indicator. It forms yellow-colored salts with copper, mercury, silver, gold, palladium, and platinum.

---

[54] SUTER and JOHNSON, *Rec. trav. chim.*, **49**, 1066 (1930).

[55] HOOPER and JOHNSON, *J. Am. Chem. Soc.*, **56**, 470 (1934).

[56] HINEGARDNER and JOHNSON, *ibid.*, **52**, 3724 (1930).

[57] JULIAN and STURGIS, *J. Am. Chem. Soc.*, **57**, 1126 (1935).

Rhodanine has an active methylene group and therefore condenses readily under the influence of acetic anhydride and sodium acetate with compounds that have an active carbonyl group (see list in Table III).

TABLE III.—CONDENSATION PRODUCTS OF RHODANINE WITH ALDEHYDES

Compounds[58]	M.p., °C.	Compounds[59]	Sintering or decomposition point, °C.
Acetaldehyde	143	Benzaldehyde	200
Crotonaldehyde	189	Furfuraldehyde	204
Isovalerylaldehyde	83	Anisaldehyde	130–142
Phenylacetaldehyde	217	Piperonal	245
Glyoxylic acid	225 d.	Dimethylaminobenzaldehyde	200

The yellow compounds thus derived from aliphatic aldehydes melt sharply, those from aromatic aldehydes usually sinter and decompose. The dimethylaminobenzylidene compound gives colors with copper,[60] mercury, and silver salts.[61] The color is one of the most sensitive tests for silver.

The condensation products with isatin,[62] phenanthraquinone,[63] alloxan,[63] thioisatinanilide,[64] and *p*-nitrosodimethylaniline[65] are generally darker than those with the aldehydes, particularly in the case of the isatin derivatives, which are red-brown to black.

Oxidation of rhodanine with ferric chloride gives rhodanine red,[66a] $C_9H_5O_3N_3S_5$, a trimeric condensation product, the formation of which may involve the active methylene group (compare with indoxyl) and the sulfhydryl group.

Rhodanine and 5-substituted rhodanines are sources of open-chain compounds.[57,58] Alkali opens the ring and forms an α-thiohydroxy unsaturated acid that exists in equilibrium with the keto form. This compound, in turn, undergoes a number of transformations as shown below.

---

[58] GRÄNACHER, GERO, OFNER, KLOFFENSTEIN, and SCHALLER, *Helv. Chim. Acta*, **6**, 458 (1923).

[59] ANDREASCH and ZIPSER, *Monatsh.*, **24**, 499 (1903); **26**, 1191 (1905).

[60] KOLTHOFF, *J. Am. Chem. Soc.*, **52**, 2222 (1930).

[61] FEIGL, *Z. anal. Chem.*, **74**, 380 (1928).

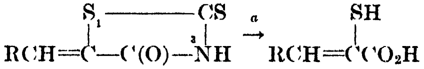
[62] ANDREASCH, *Monatsh.*, **38**, 121 (1917).

[63] BUTSCHER, *ibid.*, **32**, 96 (1911).

[64] FELIX and FRIEDLÄNDER, *ibid.*, **31**, 55 (1910).

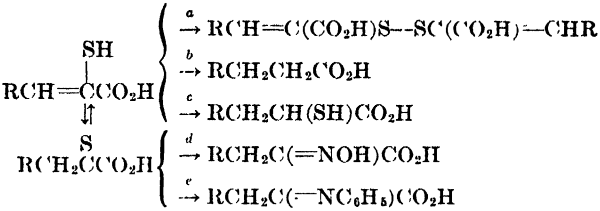
[65] KUČERA, *ibid.*, **35**, 137 (1914).

[66a] NENSKI, *J. prakt. Chem.* [2], **16**, 1 (1877).



$$\text{RCH}{=}\text{C}\underset{1}{\text{(S)}}\text{—C(O)—}\underset{3}{\text{NH}}\text{—CS} \xrightarrow{a} \text{RCH}{=}\text{C(SH)CO}_2\text{H}$$

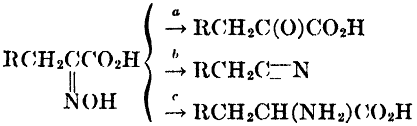
[a] NaOH or $Ba(OH)_2$.



$$\text{RCH}{=}\text{C(SH)CO}_2\text{H} \rightleftarrows \text{RCH}_2\text{C(=S)CO}_2\text{H} \begin{cases} \xrightarrow{a} \text{RCH}{=}\text{C(CO}_2\text{H)S—SC(CO}_2\text{H)}{=}\text{CHR} \\ \xrightarrow{b} \text{RCH}_2\text{CH}_2\text{CO}_2\text{H} \\ \xrightarrow{c} \text{RCH}_2\text{CH(SH)CO}_2\text{H} \\ \xrightarrow{d} \text{RCH}_2\text{C(=NOH)CO}_2\text{H} \\ \xrightarrow{e} \text{RCH}_2\text{C(=NC}_6\text{H}_5\text{)CO}_2\text{H} \end{cases}$$

[a] $FeCl_3$. [b] Zn + HCl. [c] NaHg. [d] H_2NOH. Phenylhydrazine and hydrazine give similar products. [e] $C_6H_5NH_2$.

The oxime derivative, in turn, undergoes additional useful chemical changes.



$$\text{RCH}_2\text{C(=NOH)CO}_2\text{H} \begin{cases} \xrightarrow{a} \text{RCH}_2\text{C(O)CO}_2\text{H} \\ \xrightarrow{b} \text{RCH}_2\text{C}{\equiv}\text{N} \\ \xrightarrow{c} \text{RCH}_2\text{CH(NH}_2\text{)CO}_2\text{H} \end{cases}$$

[a] HCl + H_2CO. [b] Ac_2O. [c] NaHg.

Besides its value as a reagent for preparing noncyclic compounds, rhodanine is useful in making chemical sensitizers for emulsions.

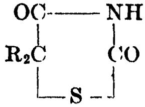
N-phenylrhodanine is derived from phenylisothiocyanate and thioglycolic acid (see page 430). The yellow colored compound melts at 194 to 195°. It is insoluble in water and ligroin, slightly soluble in

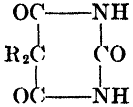
TABLE IV.—CONDENSATION PRODUCTS OF AROMATIC ALDEHYDES WITH N-PHENYL- AND N-ALLYLRHODANINE

Aldehyde	From N-phenylrhodanine, m.p., °C.	From N-allylrhodanine, m.p., °C.
Anisaldehyde	221°	114^c
Benzaldehyde	186	144
Cinnamaldehyde	217	166
Cumaldehyde	204	
Dimethylaminobenzaldehyde	235	
Furfural	183°	
o-Nitrobenzaldehyde	238	73
Piperonal	193	151
Salicylaldehyde	179	
m-Tolualdehyde	220	

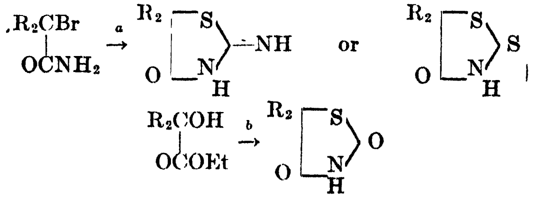
ether, and easily soluble in hot acetone, chloroform, and acetic acid. It possesses the general properties of rhodanine, such as ring opening, although, of course, it lacks the high acidity of the parent compound. The condensation products with aldehydes (Table IV) melt at lower temperatures than do the corresponding compounds from rhodanine because hydrogen bonding is no longer possible.[66b]

Dialkylthiazolones and Related Compounds.—These compounds[67] (2,4-dioxo-5,5′-dialkylthiazolidines) have some structural similarity (see below) to the dialkylbarbiturates and possess also some hypnotic


Thiazolones


Barbiturates

activity. Compounds of this type are prepared by the condensation of dialkylbromoacetic acids and thiourea as shown in the first of the equations below. Similar condensations, which employ ammonium dithiocarbamate (from carbon disulfide and ammonia) and guanidine, with appropriate amides or esters, give related derivatives of rhodanine and oxazolidine.



[a] $H_2NC(S)NH_2$ or $H_2NC(S)SH$, respectively. The first product is hydrolyzed readily. [b] $H_2NC(=NH)NH_2$.

Benzothiazole (b.p. 231° (corr.)/760 mm.) is obtained from *o*-aminothiophenol and aqueous formaldehyde.[68] It is difficultly soluble in water, but easily soluble in alcohol and carbon disulfide. It is unaffected by heating with copper.[69] Phosphorus pentachloride at 160° forms the 2-chloro-derivative,[69] nitric–sulfuric acid[70] gives the 6-nitro product, fuming sulfuric acid yields the 4-, 6-, and 7-sulfonic acids,[71] hydroxyl amine[72] or sodamide[73] forms the 2-amino compound, and benzoyl chloride and sodium hydroxide cleave the compound to N-dibenzoyl-2-aminothiophenol. Benzothiazole causes a dermititis similar to that of poison ivy. Blondes appear more susceptible than brunettes to its action.[69]

[66b] Andreasch and Zipser, *Monatsh.*, **24**, 499 (1903); **26**, 1191 (1905); Nagele, *ibid.*, **33**, 941 (1912); Holmberg and Psilanderhieln, *J. prakt. Chem.* [2], **82**, 440 (1910).

[67] Erlenmeyer and v. Meyenburg, *Helv. Chim. Acta*, **20**, 1388 (1937); Erlenmeyer and Kleiber, *ibid.*, **21**, 111 (1938).

[68] Bogert and Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925); Hofmann, *Ber.*, **13**, 8 (1880).

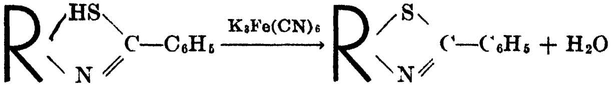
[69] Bogert and Husted, *J. Am. Chem. Soc.*, **54**, 3395 (1932).

[70] Jacobson and Kwaysser, *Ann.*, **277**, 237 (1893).

[71] Rassow, Dohle, and Reim, *J. prakt. Chem.* [2], **93**, 183 (1916).

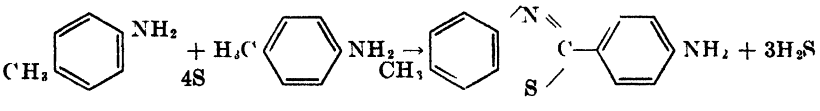
α-Naphthothiazoles[74] form more readily than the corresponding benzothiazoles. For example, the ratio of yields of the 2-chloro-derivative from the arylthiocarbimides and phosphorus pentachloride is 62 : 15, and that of the 2-ethoxy product from arylthiourethanes by oxidation with potassium ferricyanide is 60 : 40. Moreover, if 5-phenyl-β-naphthylthiocarbamide is treated with bromine, the product is exclusively 1-aniline-α-naphthothiazole with no trace of the isomeric benzothiazole.

2-Phenylbenzothiazole (m.p. 115°) can be prepared by oxidation of the thioanilide of benzoic acid. The compound has the odor of tea roses.



The *p*-tolyl homologue (m.p. 85°) has a similar but fainter odor.[75]

Dehydrothiotoluidine[76] is obtained as one of the products of heating *p*-toluidine with sulfur at 180°. It melts at 190 to 191° and boils at 434° with very little decomposition. It is very soluble in acetic acid, moderately so in hot amyl alcohol, less so in ethyl alcohol, and sparingly soluble in benzene. Its alcoholic and aqueous solutions have a beautiful violet-blue fluorescence. The dihydrochloride is obtained from hydrochloric acid. Dehydrothiotoluidine irritates the skin of some people. The compound is the source of several dyes such as columbia yellow or



thioflavine T.

Primuline base[77] is formed simultaneously with dehydrothiotoluidine and can be obtained from the latter by fusion with more sulfur. It is a higher molecular weight product of the same type as dehydrothiotoluidine. The bright yellow powder is nearly insoluble in all solvents. It may be heated to 400° without decomposition. Sulfonation converts it to an aminosulfonic acid which dissolves in hot water. This sulfonated product dyes unmordanted cotton a primrose yellow color. Hence its name, from primula, the primrose. While combined on the fiber, it can be diazotized and coupled with phenols and amines to give azo colors. Because they are produced on the fiber, they are called "ingrain" colors. All such ingrain colors are reduced to the original primulin by boiling with a solution of sodium hydrosulfite.

---

[72] Skraup, *Ann.*, **419**, 1 (1919).

[73] Ochiai and Nisizawa, *J. Pharm. Soc. Japan*, **60**, 132 (1940); *C.A.*, **34**, 5082 (1940).

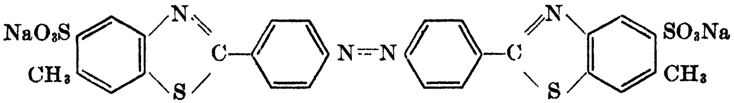
[74] Hunter and Jones, *J. Chem. Soc.*, 941 (1930).

[75] Bogert and Meyer, *J. Am. Chem. Soc.*, **44**, 1568 (1922).

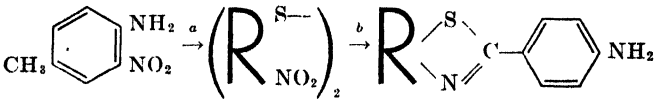
[76] Green, *J. Chem. Soc.*, **55**, 227 (1889); *Ber.*, **22**, 968 (1889).

[77] Green, *J. Soc. Chem. Ind.*, **7**, 180 (1888).

Columbia yellow is the azo dye derived from dehydrothiotoluidine by sulfonation and oxidation. The dye is known by a number of names such as chloramine yellow, Schultz No. 617. It is prepared from the sodium sulfonate of dehydrothiotoluidine and sodium hypochlorite.[78] Dyes made from dehydrothio-*m*-xylidine and dehydrothiopseudocumidine give redder shades.

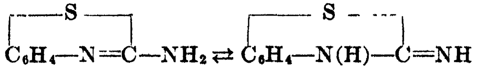


Structures of the type of columbia yellow can be made by the independent and confirmatory synthesis[79] shown below.



[a] HNO_2, I_2, Na_2S_2 in hot alcoholic solution (this process is common in the preparation of *o*-thiophenols). [b] Zn dust in boiling CH_3CO_2H, *p*-$NO_2C_6H_4COCl$ at 200°, Sn + HCl, H_2SO_4. This final product is converted to the azo dye, R—N═N—R (R = $C_{14}H_{10}NS_2O_3$) by treatment with NaOCl in Na_2CO_3 solution.

2-Aminobenzothiazole is prepared by the action of bromine on phenylthiourea or of alcoholic ammonia at elevated temperature on 2-chlorobenzothiazole. The compound has an interesting tautomerism. Methylation with methyl iodide takes place on the ring nitrogen, for the



$$C_6H_4—N{=}C—NH_2 \rightleftarrows C_6H_4—N(H)—C{=}NH$$

product is identical with that produced from *as*-methylphenylthiocarbamide and bromine;[80] diazotization and coupling with β-naphthol takes place at the 2-amino group. 2-Aminobenzothiazoles cause local anesthesia.[81]

Paper impregnated with 2-aminobenzothiazoles is used in legal documents or checks as safety paper because ink eradicators, which usually contain sodium hypochlorite, develop a red-colored blot almost instantly when applied. The color is caused by an azo dye,[82] analogous to columbia yellow. The acetyl or benzoyl derivatives of aminobenzothiazole will

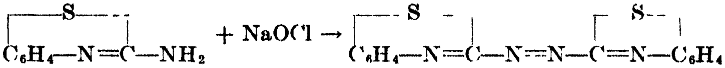
---

[78] Bogert, *Proc. Nat. Acad. Sci.*, **10**, 318 (1924).

[79] Bogert and Allen, *Ind. Eng. Chem.*, **18**, 532 (1926).

[80] Hunter, *J. Chem. Soc.*, 1385 (1926).

[81] Rose, Shonle, and Chen, *Pharm. Arch.*, **11**, 81 (1940); *C.A.*, **35**, 1522 (1941).



$C_6H_4—N=C—NH_2 + NaOCl \rightarrow C_6H_4—N=C—N=N—C=N—C_6H_4$

not form the color; but the 2-acetylamino-6-methylbenzothiazole continues to give a characteristic red-brown precipitate, presumably because the acetyl group is removed in the alkaline solution.

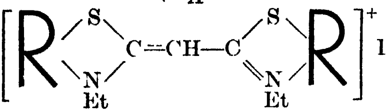
An independent synthesis,[82] which comprises the steps—2-aminobenzothiazoles to the diazonium fluoborates, to the 2-nitro compounds, to the amino compounds, to the azo dyes—confirms the structure of these dyes. Reduction of the nitro compound (*a*) by tin and hydrochloric acid gives the original amine and (*b*) by dextrose gives the azoxy product.

$$RTNH_2 \rightarrow RTN_2BF_4 \rightarrow RTNO_2 \rightarrow RTNH_2 \rightarrow RTN{=}NTR$$

T = benzothiazole nucleus. R = 6-methyl, 4-methyl, 6-ethoxy, 6-chloro, or 6-bromo.

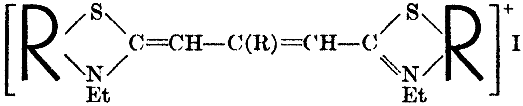
Cyanine Dyes in the Thiazole Series.—Cyanine dyes result when benzothiazole ethiodide is heated with 2-methylbenzothiazole ethiodide in pyridine. A mixture of a yellow-colored thiacyanine (*A*) and, in smaller amount, a purple-colored thiacarbocyanine (*B*) (R=H) is obtained.[83] The extra carbon atoms in the carbocyanine salt come from

A



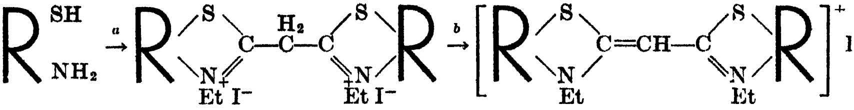
3,3′-Diethylthiacyanine iodide

B



3,3′-Diethylthiacarbocyanine iodide

decomposition (breaking out of the substituted 2-carbon atom) of the benzothiazole salt.[84] If the 2-methylbenzothiazole ethiodide is heated alone, a different thiacarbocyanine dye is obtained, one with a side methyl group (R=CH_3, in *B*). The constitution of *A* is established[83] by a sequence of reactions from *o*-aminophenyl mercaptan.



[a] $H_2C(CO_2Et)_2$, EtI at 100° in order to form the diethiodide salt. [b] 16 per cent NaOH in order to eliminate HI, EtI at 100°.

---

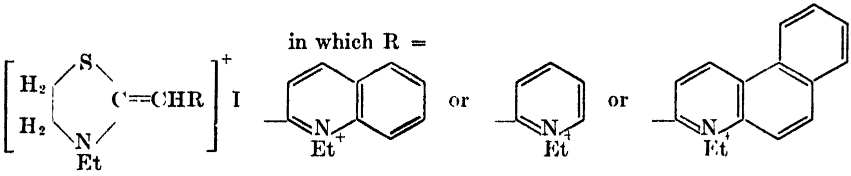
[82] Kirk, Johnson, and Blomquist, *J. Org. Chem.*, **8**, 557 (1943).

[83] Mills, *J. Chem. Soc.*, **121**, 455 (1922).

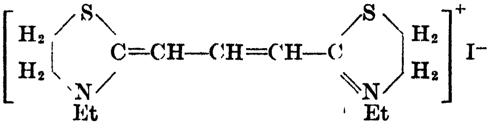
[84] Brooker and White, *J. Am. Chem. Soc.*, **57**, 547 (1935).

The thiacarbocyanines are obtained by heating 2-methylbenzothiazole ethiodide or, better, the etho-*p*-toluenesulfonate in anhydrous pyridine, preferably with some triethylamine or piperidine.

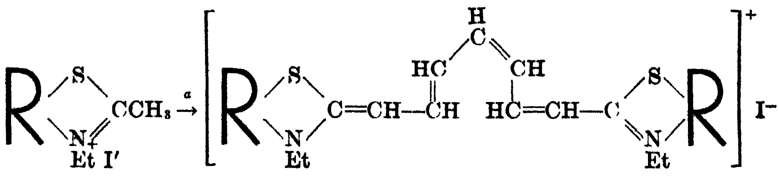
2-*Methylthiazolines*, prepared by treatment of N-acyl-2-aminoethanol with phosphorus pentasulfide, have a methyl group activated by an adjacent C=N system. Hence the methyl group is active enough to undergo the common cyanine dye formations when the quaternary salt is heated in the presence of triethylamine with 2-iodoquinoline ethiodide, 2-iodopyridine ethiodide, or with 3-iodobenzo[*f*]quinoline ethiodide.[85] The corresponding cyanine iodide products are indicated below and are called



1′,3-diethylthiazolino-2′-cyanine iodide, 1′,3-diethylthiazolino-2′-pyridocyanine iodide, and 1′,3-diethyl-5′,6′-benzothiazolino-2′-cyanine iodide, respectively. 2-Methylthiazoline ethiodide condenses with ethyl orthoformate. The product is 3,3′-diethylthiazolinocarbocyanine iodide.



When 2-methylbenzothiazole ethiodide and dinitrophenylpyridinium chloride are boiled together with alcoholic sodium alkoxide for a short time, a 3,3′-diethylthiatricarbocyanine iodide is formed.[86] The pyridinium salt acts so as to provide glutaconaldehyde *in situ*. The reaction is shown below.



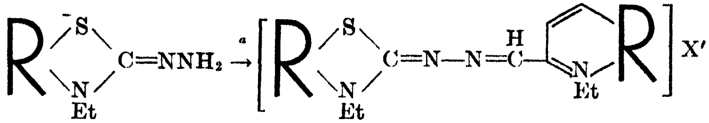
[a] Heated with alcoholic sodium alkoxide and 2,4-dinitrophenylpyridinium chloride. See page 200 for the formation of glutaconaldehyde.

---

[85] Brooker, *ibid.*, **58**, 662 (1936).

[86] Fisher and Hamer, *J. Chem. Soc.*, 189 (1933).

Unsymmetrical azo dyes[87] of a similar type can be obtained by the reaction shown below.



The N-ethylbenzthiazolone hydrazone is prepared from ethylphenylthiourea, $C_6H_5N(C_2H_5)C(S)NH_2$, and bromine in chloroform, followed by treatment of the product with sodium nitrite and reduction of the diazonium compound with zinc dust and acetic acid. This hydrazone is then condensed (*a*) with an anil of the aldehyde from quinaldine methiode by heating in aqueous perchloric acid solution. The anil is prepared from the reaction of quinaldine methiodide and *p*-nitrosodimethylaniline in the presence of piperidine.

2-*Mercaptobenzothiazole*.—This compound, known commonly as Captax, was first made[88] in 1887 in an attempt to prepare a thiocarbanilide derivative from carbon disulfide and *o*-aminophenol. Its use as a vulcanization accelerator[89] came from the discovery that the product of reaction between thiocarbanilide, an accelerator, and sulfur was itself a valuable accelerator. This thiazole compound has now come to be one of the important agents in accelerating vulcanization.

The numerous methods for preparation of 2-mercaptobenzothiazole emphasize the great tendency for the thiazole ring to form. Aniline, carbon disulfide, and sulfur at 200 to 275°,[90] aniline, formamide, and sulfur[91] at 195°, zinc aryldithiocarbamate, $(C_6H_5NHC(S)S)_2Zn$, and sulfur[92] produce the compound probably through an ortho thiol derivative as an intermediate. Thiocarbanilide, $(C_6H_5NH)_2CS$, and sulfur[92] have been used. Azobenzene[93] and carbon disulfide at 260 to 270° also form the compound. The preparation from 2-chlorobenzothiazole and sodium sulfide locates the position of the mercapto group.

The compound melts at 179° and undergoes the usual reactions of a thiol. Oxidation[88] with potassium dichromate gives a disulfide $C_7H_4NS{\cdot}S{-}S{\cdot}C_7H_4NS$, methylation yields the S-methyl thio ether, fusion[93] with potassium hydroxide give *o*-aminophenol, treatment of the ammonium salt with ammonium zincate gives the zinc salt, reaction of an alcoholic solution with a soluble lead salt gives the lead salt.[91] Its role in vulcanization may be to promote a change of sulfur to an active state. Numerous derivatives such as the hydroxymethyl, $RSCH_2OH$ ($R = C_7H_4NS$), the phenylaminomethyl, $RSCH_2NHC_6H_5$, the benzoyl, $RSCOC_6H_5$, the disulfide RSSR, and the zinc salt have been tested also as accelerators.

---

[87] FUCHS and GRANAUG, *Ber.*, **61**, 57 (1928).

[88] HOFMANN, *ibid.*, **20**, 1788 (1887).

[89] For accounts of organic accelerators see GEER and BRADFORD, *Ind. Eng. Chem.*, **17**, 393 (1925); SHEPARD, *ibid.*, **25**, 35 (1933); TRUMBULL, *ibid.*, **25**, 230 (1933); OENSLAGER, *ibid.*, **25**, 232 (1933).

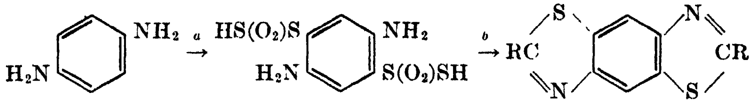
[90] British patent 335,567 (1929); *C.A.*, **25**, 1539 (1931). U. S. patent 1,911,716 (1938); *C.A.*, 27, 3952 (1933).

[91] SEBRELL and BOORD, *J. Am. Chem. Soc.*, **45**, 2390 (1923); MAGEL, *Ind. Eng. Chem.*, **26**, 611 (1934).

[92] BEDFORD and SEBRELL, *ibid.*, **13**, 1034 (1921).

[93] JACOBSON and GRANKENBACKER, *Ber.*, **24**, 1400 (1891).

2,6-*Diphenylbenzo*-1,2,3,4-*bisthiazole.*—This condensed system (m.p. 232 to 234°) is prepared by conventional processes from *p*-phenylene diamine by way of *p*-phenylene-2,5-di(thiosulfonic acid).[94] Steps are shown below.

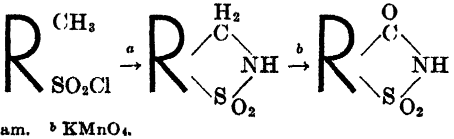


$R = C_6H_5$.

[a] Alkaline solution of sodium thiosulfate and sodium chromate. [b] Condensation with benzaldehyde.

If acetic anhydride and sulfuric acid had been used in place of benzaldehyde, the product would have been a dimethyl-substituted compound (m.p. 98 to 100°). Nitrous acid and the dithiosulfonic acid give the di-diazosulfide which melts at 224 to 226° d. and explodes with violence above that temperature.

Saccharin is a nontoxic and nonnutritive sweetening agent, which is used as a substitute for sugar, particularly by diabetic patients. It was discovered in the course of a study by Remsen and Fahlberg when the latter happened to eat without washing his hands and observed an unusually sweet taste in the bread that he handled. The compound is prepared by treatment of *o*-toluenesulfonyl chloride and ammonium carbonate with steam and then oxidization of the sulfonamide with potassium permanganate. It is purified by solution in alkali and reprecipitation with acid.



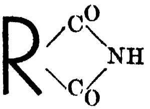
[a] $(NH_4)_2CO_3$ and steam. [b] $KMnO_4$.

Methyl- and ethyl-saccharins[95] have a taste comparable to saccharin. 6-Aminosaccharin is sweeter; 6-nitrosaccharin is extremely bitter. The taste of a number of compounds whose structure bears some relation to that of saccharin is indicated below.

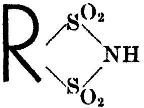
---

[94] Green and Perkin, *J. Chem. Soc.*, **83**, 1201 (1903).

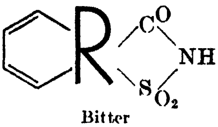
[95] Dyson, *Chem. Age* (*London*), **11**, 572 (1924).



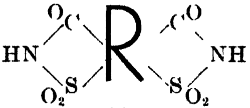
Tasteless



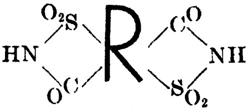
Half, as sweet as saccharin



Bitter



Bitter



Sweetish astringent

Large R represents C_6H_4 or C_6H_3.

The sweetness of saccharin, compared with sugar, increases with dilution.[96] It is 190 times as sweet at 5 parts to 6,400 and 675 times as sweet at 5 parts to 204,800.

PYRAZOLE COMPOUNDS

The first pyrazole compound was prepared by Knorr,[97] in 1883, from phenylhydrazine and a β-keto ester. The presence of nitrogen suggested a relationship to quinine and led to tests on the antifebril properties of some of its derivatives. The discovery in 1884 of the important medicinal, antipyrin, created a great interest in this field which continues even today. The total number of pyrazole compounds is, accordingly, very large.

Dimethylpyrazole is obtained by condensing acetylacetone with hydrazine hydrate.[98] It melts at 107° and boils at 220° (corr.). The compound has some interest in quantitative analysis because it forms a beautiful purple precipitate with cobalt from a slightly alkaline solution.[99]

Acyl Pyrazoles.—3-Substituted or unsymmetrically 3,5-disubstituted pyrazoles form two acetyl compounds.[100] The stable isomer is prepared from the reaction of a substituted pyrazole with acetyl chloride in pyridine for an hour at ice temperature and then at room temperature; the labile one is obtained from the reaction of a 1,3-diketone in a concentrated alcoholic solution with the acethydrazide for 3 hr. at 40 to 50°, followed by treatment in the cold of the hydrazone with phosphoryl chloride. The labile compound may sometimes be converted to the stable one by boiling under diminished pressure for 15 or 20 min. and then distilling. The melting points of some of these N-substituted compounds are shown below.

---

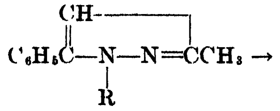
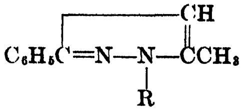
[96] Magidson and Gorbachov, *Ber.*, **56**, 1810 (1923).

[97] Knorr, D. R. P. 26,429; *Ber.*, **16**, 2597 (1883).

[98] Knorr and Rosengarten, *Ann.*, **279**, 237 (1894).

[99] Heim, *Ind. Eng. Chem.*, *Anal. Ed.*, **2**, 38 (1930).

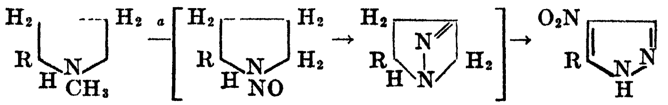
[100] v. Auwers and Dietrich, *J. prakt. Chem.*, **139**, 65 (1934).

R		
$CH_3C(O)$	45.5–46.5	41°
$CH_3CH_2C(O)$	33–34	77–78.5
$CH_3CH_2CH_2C(O)$	34–35.5	72–72.5
$C_6H_5CH_2C(O)$	104.5–105.5	58–59.5
$C_6H_5OC(O)$	65–66	73.5–74.5
$C_6H_5C(O)$	88–90	83–84
o-$CH_3C_6H_4C(O)$	63–65	36.5–37.5
m-$CH_3C_6H_4C(O)$	79–80	56–57
p-$CH_3C_6H_4C(O)$	83–85	68–70
o-$NO_2CH_3C_6H_4C(O)$	157–157.5	107–108
$H_2NC(O)$	....	154–156°

Chloroacetylpyrazole, like many other chloroacetyl compounds, is a powerful lachrymator.[101] It is prepared from N-pyrazolemagnesium halide with chloracetyl chloride at 60°.

Pyrazole Carboxylic Acids.—The general processes for obtaining pyrazole carboxylic acids or the corresponding esters are by condensation of a hydrazine with an acetyl, benzoyl, or other derivative of ethyl acetoacetate, by addition of a hydrazine to an ethylidene derivative of ethyl acetoacetate or like compound, by oxidation of a side chain, or by other standard methods. A number of acids are listed in Table V, in order to show some common types and to illustrate the methods of preparation.

4-Nitro-5-(3-pyridyl)-pyrazole is formed as a by-product in about 5 per cent yield during the nitric acid oxidation of nicotine to nicotinic acid.[102] A possible sequence of key compounds, shown below, may account for the occurrence of this by-product.



R = 3-pyridyl radical.

[a] Nitric acid is assumed to oxidize the methyl group to a carboxyl group. Loss of carboxyl gives a secondary amine which forms an N-nitroso compound. An intramolecular condensation gives a bicyclic product. A series of oxidation, decarboxylation, and nitration can be assumed to occur.

The pyrazole ring is probably formed without prior rupture of the cyclic structure. Otherwise nicotinic acid would be formed.

Pyrazolines of the 3-alkylamino type have some interest as local anesthetics. 1-Phenyl-5-p-anisyl-3-β-piperidinoethylpyrazoline and

---

[101] Mingoia and Ingraffia, *Gazz. chim. ital.*, **64**, 279 (1934).

[102] Gough and King, *J. Chem. Soc.*, 2968 (1931); 2768 (1932); 350 (1933).

TABLE V.—CARBOXYLIC ACIDS IN THE PYRAZOLE SERIES

—Carboxylic acid	M.p., °C.	Ester type[a]	M.p., °C.	Prep.	Ref.
N-Pyrazole	103 d	..	......	1	103
Pyrazole-3-	214 d	..	....	2	104
Pyrazole-4-	275 d	..	....	3	105
5-Methylpyrazole-3-	236 d	E	82 83	4	104
4-Methylpyrazole-3-	220	M	170 171	5	106
3-Methylpyrazole-4-	228 d	E	54	6	106,107
3,5-Dimethylpyrazole-4-	200 d	E	96	7	98,104
Pyrazole-3,4-di-	260 d	..	....	8	108
Pyrazole-3,5-di	289 d	..	....	9	104
Pyrazole-3,4,5-tri	233 d	..	....	10,11,12	104,109, 110,111
1-Phenylpyrazole-3-	146	M	77	13	112
1-Phenylpyrazole-4-	221	M	129	13	112
1-Phenylpyrazole-5-	183	M	67	13	112
1-Phenyl-5-methylpyrazole-3	136	M	56	14	113
1-Phenyl-4-methylpyrazole-3	134	..	....	15	112,114
1-Phenyl-3-methylpyrazole-4	193	..	.....	16	11,13,14, 112,114,115
1-Phenyl-5-methylpyrazole-4	168	M	71	17	114
1-Phenyl-3-methylpyrazole-5	190	M	66	18	112
1-Phenyl-3,5-dimethyl-pyrazole-4-	198	E	70	19	116
1-Phenylpyrazole-3,4-di-	200.5	M	75	20	114
1-Phenylpyrazole-3,5-di-	266	M	128	21	112,114
1-Phenylpyrazole-4,5-di-	216	M	76	20	114
4-Phenylpyrazole-3,5-di-	246 d	..	...	22	116
5(3)-Phenylpyrazole-3,4(4,5)-di-	235 d	..	......	22	117
1-Phenyl-5-methylpyrazole-3,4-di	198 d	..	....	23	118
1-Phenyl-3,4,5-tri-	184	..	......	24	118
1,3-Diphenyl-5-methyl-pyrazole-4-	205	E	122	25	119
1,3-Diphenylpyrazole-4,5-di	218	..	....	26	118

[a] M = methyl; E = ethyl.

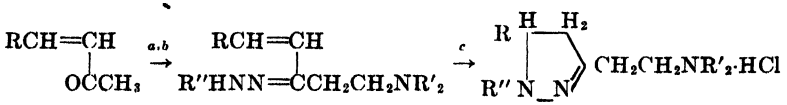
Preparation

When the reagents mentioned are such as to produce the ester, the acid has been obtained by saponification. The listing of the reagents is such as to indicate the primary source of the compound as far as possible.

1. Pyrazylmagnesium halide and ethyl chloroformate.
2. 3-Methylpyrazole and potassium permanganate.

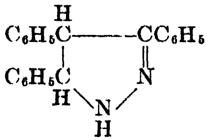
[103] MINGOIA, *Gazz. chim. ital.*, **61**, 449 (1931).
[104] KNORR and coworkers, *Ann.*, **279**, 217 (1894).
[105] BEHAGHEL and BUCHNER, *Ber.*, **35**, 34 (1902).
[106] v. PECHMANN and BURKHARD, *ibid.*, **33**, 3597 (1900).
[107] DAINS and HARGER, *J. Am. Chem. Soc.*, **40**, 562 (1918).
[108] v. PECHMANN, *Ber.*, **33**, 627 (1900).
[109] BUCHNER, *ibid.*, **22**, 842 (1889).
[110] HURD and LUI, *J. Am. Chem. Soc.*, **57**, 2656 (1935).
[111] BUCHNER, and HEIDE, *Ber.*, **34**, 347 (1901); ADAMSON and KENNER, *J. Chem. Soc.*, 286 (1935).
[112] CLAISEN, *Ann.*, **278**, 261 (1893).
[113] CLAISEN and ROOSEN, *ibid.*, **278**, 274 (1893).
[114] CLAISEN, *ibid.*, **295**, 301 (1897).
[115] BALBIANO, *Gazz. chim. ital.*, **28**, I, 382 (1898).
[116] KNORR, *Ber.*, **20**, 1096 (1887).
[117] BUCHNER and FRITSCH, *ibid.*, **26**, 257 (1893).
[118] KNORR and LAUBMANN, *ibid.*, **22**, 172 (1889).

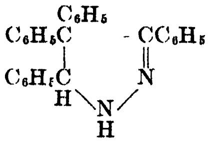
1-phenyl-5-*p*-anisyl-3-β-di-*n*-propylaminoethylpyrazoline and 1-phenyl-5 (4′-methoxy-3′ethoxvphenyl)-3-β-piperidinoethylpyrazoline hydrochloride are five to ten times more effective, although a little more toxic, than cocaine. They are prepared[119] by a sequence of (*a*) condensation of benzylideneacetone and formaldehyde with dimethylamine (Mannich reaction), (*b*) hydrazone formation with the resulting ketone, and (*c*) isomerization of the product to a pyrazoline in hot glacial acetic acid.



R = phenyl or 4-methoxy-3-ethoxyphenyl or anisyl. R′ = propyl or piperidino. R″ = phenyl.

Tri- and Tetra-phenylpyrazoline.—By a succession of reactions, benzylmagnesium chloride or benzyllithium reacts with 2 molecules of benzonitrile to give a triphenylpyrazoline; diphenylmethylsodium acts similarly to form a tetraphenypyrazoline.[120] Both compounds





are converted to pyrazoles by oxidation with chromic acid. The tetra-

---

3. 4-Phenylpyrazole and a sequence of nitration to a dinitrophenylpyrazole, reduction with tin and hydrochloric acid, and permanganate oxidation.
4. The product from ethyl oxalate and acetone treated with hydrazine.
5. Methyl crotonate and diazomethane followed by oxidation with bromine.
6. Diethyl citraconate and diazomethane followed by oxidation with bromine.
7. Ethyl acetylacetoacetate and hydrazine.
8. Pyrazolindimethylenpicryl acetate ($C_{11}H_{11}O_8N_5$ from diazomethane and picryl acetate) oxidized by nitric acid.
9. 3-Methylpyrazole-5-carboxylic acid and potassium permanganate.
10. Ethyl acetylenedicarboxylate and ethyl diazoacetate.
11. Diethyl maleate and ethyl diazoacetate followed by mild oxidation.
12. Ethyl diazoacetate (3 molecules) with itself followed by oxidation with bromine.
13. 1-Phenyl-3-methylpyrazole and potassium permanganate.
14. (The acid from ethyl oxalate and acetone) and phenylhydrazine.
15. 1-Phenyl-3,4-dimethylpyrazole and permanganate.
16. Aldehydobutanone (from methyl ethyl ketone, ethyl formate, and sodium ethoxide) and phenylhydrazine followed by oxidation with bromine.
17. Ethyl aldehydoacetoacetate (from ethyl acetoacetate and ethyl formate) and phenylhydrazine.
18. Acetoneoxalic acid and phenylhydrazine (minor product).
19. Ethyl acetylacetoacetate and phenylhydrazine.
20. 1-Phenyl-5-methylpyrazole-4-carboxylic acid and permanganate.
21. 1-Phenyl-5-methylpyrazole-3-carboxylic acid and potassium permanganate.
22. Methyl phenylpropiolate and methyl diazoacetate at 80 to 90°.
23. 1-Phenyl-3,5-dimethylpyrazole-4-carboxylic acid and potassium permanganate.
24. 1-Phenyl-3-methyl-4,5-dicarboxylic acid and potassium permanganate.
25. Ethyl benzoylacetoacetate and phenylhydrazine.
26. 1,3-Diphenyl-4,5-dimethylpyrazole and potassium permanganate.

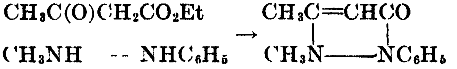
[119] Nisbet, *ibid.*, 1237, 1568 (1938).

[120] Anker and Cook, *ibid.*, 323 (1941).

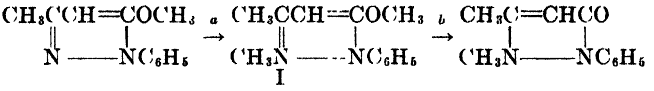
phenyl compound can be prepared also by interaction of stilbene with diphenyldiazomethane.

1-*Phenyl-3-methyl-5-pyrazolone.*—This azolone is the starting point for preparing many interesting and useful compounds. It is made from phenylhydrazine and ethyl acetoacetate.[97] It melts at 116°; boils at 333°; is soluble in acids, hot alcohol, or chloroform. One gram dissolves in 50 cc. of boiling water, 20 cc. of boiling ether, and 2 cc. of boiling benzene. The copper salt (CuP_2, P for the pyrazolone) is cocoa brown and melts at 185°; the iron salt (FeP_3) is violet tinged with gray and melts at 198°; the cobalt (CoP_2) is ultramarine blue; and another cobalt compound ($HOCoP_2$) is dark brown. Two silver salts, AgP and AgP_2, exist.[121]

Antipyrine.—Methylation of 1-phenyl-3-methyl-5-pyrazolone with methyl iodide and alkali in alcohol, methyl sulfate and alkali, methyl benzenesulfonate and alkali in benzene, or by methyl alcohol and hydrochloric acid gives the N-methyl derivative, known as antipyrine; methylation by diazomethane, and to a small extent by methyl iodide as a by-product, gives the O-methyl ether. The structure of the N-methyl product is shown by its synthesis from ethyl acetoacetate and methylphenylhydrazine.[122] The O-methyl may be converted to the N-methyl



derivative by addition and elimination of methyl iodide as follows.



^{a} CH_3I. ^{b} Heat with alkali.

This last reaction created some difficulty in interpreting the structure of antipyrine, since elimination of methyl iodide might join oxygen to nitrogen and produce a four-membered ring, *i.e.*, a bicyclic system. The synthesis of antipyrine from methylphenylhydrazine settled the question.

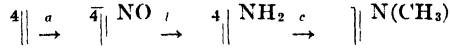
Antipyrine is used extensively as a medicinal. At the period when it was discovered, chemists were greatly interested in quinine. Knorr, in fact, regarded his compound as a "chinizin" derivative. Physiological tests showed that the compound had, indeed, a strong antipyretic action, hence the common name of antipyrine. It has no action, however, on malaria,[123] and owes its antifebril property to alteration of the regulatory body functions so that increased heat loss, rather than decreased heat production, results.[124]

---

[121] Dubsky and Wintrova, *Collection Czech. Chim. Commun.*, **11**, 526 (1939); *C.A.*, **35**, 2446 (1941).

[122] Knorr, *Ann.*, **238**, 137 (1887); **328**, 78 (1903).

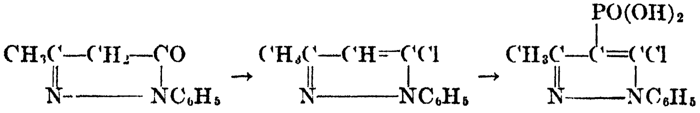
A large number of drugs contain antipyrine in molecular combination or are derivatives of that compound. Migrainin is a mixture of antipyrine, caffeine, and citric acid; ferripyrine is a styptic iron compound; chloralantipyrine is a mixture with chloral hydrate. In thiopyrine or anilinopyrine, the oxygen atom in antipyrine is replaced by a thio or anilino group. *Pyramidone* is 4-dimethylamino-1,5-dimethyl-2-phenyl-3-pyrazolone. It is derived from antipyrine by a reaction sequence at the 4-position as follows.



^{a} HNO_2. ^{b} Zn + HOAc or $H_2S + NH_3$ ^{c} CH_3I + alc KOH.

It is about three times as effective as antipyrine but is apt to cause agranulocytosis. Melubrin is the product of condensing 4-aminoantipyrine with formaldehyde bisulfite so that the substituent, $—NHCH_2-SO_3H$, is in the 4-position. It combines a mild antifebril action with low toxicity and has a specific effect in acute articular rheumatism. Novalgin is N-methylmelubrin and is more active than melubrin. Trigenin is a molecular combination of pyramidone and butylchlorohydrate. It is used as an analgesic and sedative. Compral is a combination of pyramidone and voluntal, a trichloride of ethanol.

When 1-phenyl-3-methylpyrazolone-5 is boiled with phosphorus oxychloride, the product is 5-chloro-1-phenyl-3-methylpyrazole. If heating is continued for 12 hr., condensation of the primary product with more phosphorus oxychloride occurs. The final product is 5-chloro-1-phenyl-3-methylpyrazole-4-phosphinic acid.[20]

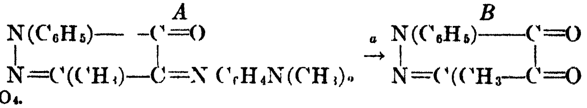


Condensation Products of the Pyrazolones.—The azolones have some of the appearance and behavior of indoxyl. The active methylene group condenses with hydroxyl amine, aldehydes, nitroso compounds, and the like. 1-Phenyl-3-methyl-pyrazolone-5 and *p*-nitrosodimethylaniline, for example, give the black-green anil (*A*) (m.p. 187°) which undergoes hydrolysis to 1-phenyl-3-methyl-4-keto-5-pyrazolone (*B*) a compound (m.p. 119°) of the isatin type, which, in turn, forms a hydrate

---

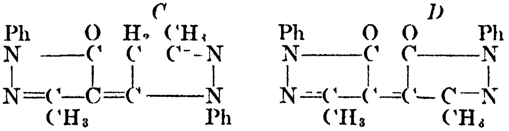
[123] GOODMAN and GILMAN, "The Physiological Basis of Therapeutics," p. 248, The Macmillan Company, New York, 1941.

[124] BOCKMÜHL, Antipyretic and Analgesics of the Pyrazolon Series, p. 155, Reports from Medico Chemical Research, I.G. Farbenindustrie Aktiengesellschaft, Leverkusen, German 1933.



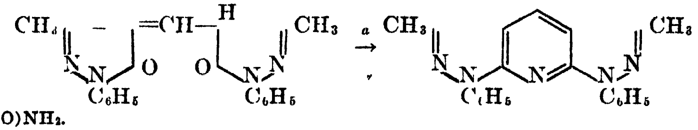
ᵃ Dilute H_2SO_4.

(m.p. 71°), an oxime (m.p. 157°), phenylhydrazone (m.p. 155°), and a bisulfite addition compound and condenses with *o*-phenylene diamine.[125] The azolone also condenses with itself under the influence of piperidine.[126] The dimer (*C*) melts at 258°; the trimer at 262°. Ferric chloride oxidizes the indoxyl-like azolone to *pyrazole blue* (*D*).[122] This last product has an absorption spectra similar to that of indigo; it forms a leuco product when reduced by sodium amalgam and alcohol, from which, in turn, the



color is restored by oxidation; it adds bromine, but loses the halogen readily by boiling alcohol, water, or ammonium sulfide; and it undergoes hydrolysis with warm concentrated hydrochloric acid to the diketo isatinlike product.

Formamide, orthoformic ester, or chloroform and alkali condenses with the active methylene group to give a dihydro-compound that readily passes to the orange-colored 4,4′-methylidenebis-(1-phenyl-3-methyl-5-pyrazolone) which melts at 181° and is claimed to be of value as a filter layer in photographic processes.[127] When this last product is heated at 200° with another molecule of formamide, a pyridine compound results from a condensation that is typical of the action of ammonia on carbonyl groups in the 1,5-position.[128]



ᵃ $HC(O)NH_2$.

Hydrogen peroxide cleaves the azolone, but the product condenses with the unaltered pyrazolone.[129] The structure of the second product is shown by a reliable synthesis from a compound derived from ethyl acetoacetate.

---

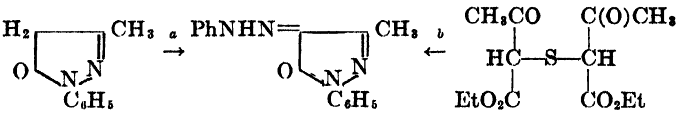
[125] Sachs and Barschall, *Ber.*, **35**, 1437 (1902).

[126] Ionescu and Georgescu, *Bull. soc. chim.* [4], **41**, 1514 (1927).

[127] Gaspar, British patent 506,385 (1939); *C.A.*, **33**, 9169 (1939).

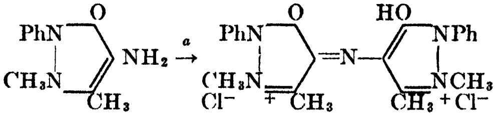
[128] Schiedt, *J. prakt. Chem.*, **157**, 203 (1940); Perroncito, *Atti X congr. intern. chim.*, **3**, 267 (1939); *C.A.*, **34**, 2842 (1940).

[129] Perroncito, *Gazz. chim. ital.*, **65**, 554 (1935); Buckka and Sprague, *Ber.*, **22**, 2541 (1889).



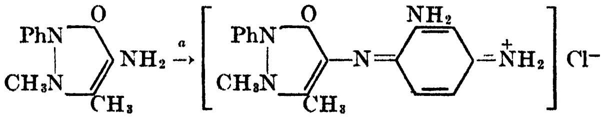
[a] H_2O_2 forms C_6H_5NHNO which then condenses with more of the azolone. [b] The thio ether reacts with 2 molecules of phenylhydrazine and forms $(C_{10}H_9N_2O)$—S—$(C_{10}H_9N_2O)$, which then reacts with more phenylhydrazine to give the desired phenylhydrazone together with H_2S and H_2 (reduction products).

Aminoantipyrine (m.p. 109.5°) is an azolone with an active carbonyl group. The compound is an intermediate in the preparation of pyramidone and is obtainable in excellent yield.[130] Ferric chloride eliminates an amino group while oxidizing the compound to *antipyrine red.*[131]



[a] $FeCl_3$.

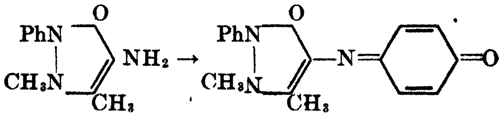
A somewhat related reaction between aminoantipyrine and *m*-phenylenediamine forms an indamine-type (see page 482) red dye.



[a] *m*-Phenylene diamine hydrochloride and ferric chloride.

The structure of the dye is shown (*a*) by the failure of like products to form when the para position of the aniline is blocked as in *p*-toluidine, *p*-phenylene diamine, or sulfanilic acid and (*b*) by the synthesis of the compound by reduction and oxidation of the product from aminoantipyrine and 2,4-dinitrochlorobenzene. Diphenyl amine produces a blue dye with aminoantipyrene.

A similar reaction occurs with phenol in the presence of an ammoniacal cupric salt or alkaline potassium ferricyanide.



The color produced is a sensitive test for phenols.[132] Phenol itself can be detected by this reaction at concentrations of 1 part in 8 million;

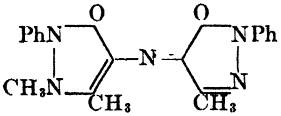
[130] EISENSTAEDT, *J. Org. Chem.*, **3**, 153 (1938).

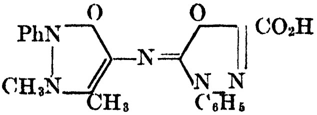
[131] MICHAELIS, *Ann.*, **352**, 157 (1907).

[132] EMERSON, *J. Org. Chem.*, **8**, 417 (1942).

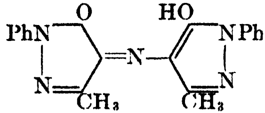
o-cresol at 1 part in 2 million, and *m*-cresol at 1 part in 6½ million. Alkyl groups in the 4-position of the phenol or amine interfere with the test. For example, *p*-cresol, 2,4-dimethylphenol, and 3,4-dimethylphenol give no test, but 3,5-dimethylphenol, 2,5-dimethylphenol, thymol, and carvacrol give strong tests. Chloro, bromo, carbonyl, sulfonic acid, hydroxyl, and methoxyl do not interfere, probably because each group is expelled. A nitro group in the ortho position prevents the reaction; one in the meta position inhibits, but does not prevent it. The coupling with aminoantipyrine always occurs in the para position.

Aminoantipyrine condenses also with 1-phenyl-3-methyl-5-pyrazolone. The methylene group behaves as does the group para to the hydroxy group in phenols. An alkyl group at C_4 stops the reaction, but a bromine atom does not. Neither do the benzylidene, isopropylidene, and isonitroso groups interfere. The behavior in this respect, save for the isonitroso group, is similar to that in 5-benzalbarbituric acid. The condensation product of aminoantipyrine with 1-phenyl-3-carboxypyrazolone-4 has an intense green color, is stable, and is insoluble in chloroform.[133]

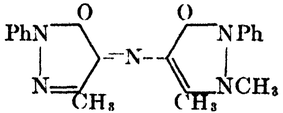




Rubazonic acid, the purpuric acid (see page 492) of the pyrazole series, forms with great ease by oxidation of phenylmethylaminopyrazolone, or by long refluxing of pyrazole blue with aqueous ammonia, or by treatment of phenylmethylnitrosopyrazolone with sodium methoxide



Rubazonic acid



Methyl rubazonic acid

and methyl iodide.[134] The compound crystallizes as red needles that melt at 181°. It is insoluble in benzene but dissolves in ammonia and dilute alkalies with a change in color from red to purple. It is found in the urine as a transformation product of pyramidone.[124]

Methyl rubazonic acid (m.p. 175 to 176°) is prepared[133,135] by condensation of 1-phenyl-3-methyl-5-pyrazolone with nitrosoantipyrine or, better, by oxidation (K_3FeCN_6) of an alkaline mixture of aminoantipyrine and 1-phenyl-3-methyl-pyrazolone-5. The acidic properties present in rubazoic acid are, of course, absent in this compound. It is insoluble in alkalies but soluble in mineral acids with decomposition. It crystallizes from methanol as transparent garnet-red prisms with a slight green reflex.

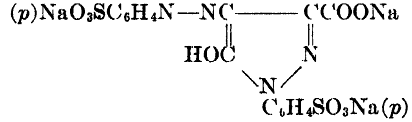
---

[133] EMERSON and BUGLE, *ibid.*, **8**, 433 (1943).

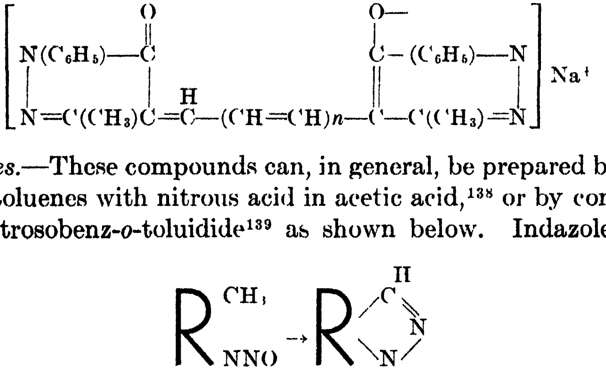
[134] KNORR, *Ann.*, **238**, 192 (1887).

[135] PRÖSCHER, *Ber.*, **35**, 1436 (1902).

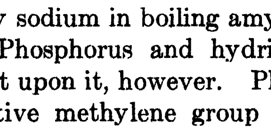
Tartrazine dyes can be obtained from the condensation of phenylhydrazine sulfonic acid and ethyl oxaloacetate, followed by hydrolysis and coupling with a diazonium salt.[136] The name is derived from the fact that this class of dyes was originally obtained from the reaction of a primary hydrazine with dehydrotartaric acid and was believed to have a structure like that of tartaric acid.[137] They have since been shown to be pyrazolone derivatives.[136] This yellow dye is one of the 15 dyes approved (in 1937) by the United States Government for use in food.



Pyrazolone dyes of the type shown below are suitable as antihalation agents in photographic processes.



Indazoles.—These compounds can, in general, be prepared by reaction of *o*-aminotoluenes with nitrous acid in acetic acid,[138] or by condensation of an N-nitrosobenz-*o*-toluidide[139] as shown below. Indazole melts at



146.5° and boils at 270°/743 mm. It crystallizes from hot water. It resists hydrolysis by concentrated hydrochloric acid and 20 per cent sulfuric acid, reduction by sodium in boiling amyl alcohol, and oxidation by Fehling's solution. Phosphorus and hydriodic acid at 250° and alkaline permanganate act upon it, however. Phenyldiazonium chloride couples with it. An active methylene group is present. Cryoscopic measurements in naphthalene show that the compound, like pyrazole, is associated.[140] Methylation or acetylation eliminates the hydrogen bond and gives products that have normal values.

---

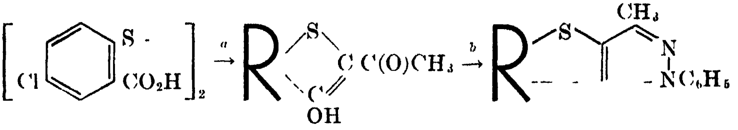
[136] Hewitt, *J. Soc. Dyers and Colourists*, **36**, 6 (1920).

[137] Anschutz, *Ann.*, **294**, 219 (1896); **306**, 1 (1899).

[138] Noelting, *Ber.*, **37**, 2556 (1904); Porter and Peterson, *Org. Syntheses*, **20**, 73 (1940).

[139] Fischer and Tafel, *Ann.*, **227**, 308 (1885).

Thionaphthenopyrazole.—Compounds[141] with condensed benzene, thiophene, and pyrazole nuclei can be obtained from 5,5′-dichloro-2,2′-dithiobenzoic acid by stepwise formation of the thiophene and pyrazole nuclei as shown below in the preparation of 7-chloro-1-phenyl-3-methyl-4,5-thionaphtheno[3,2-c]pyrazole.



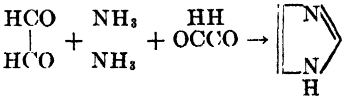
Large R = ClC_6H_3.

[a] Reaction of the disulfide with acetic anhydride and potassium acetate at 130° for 4 hr. or in concentrated sulfuric acid at 50°. [b] Refluxed in a benzene solution of phenylhydrazine.

IMIDAZOLES

In 1858, Debus[142] was engaged in a study of the reactions of ammonia on glyoxal, which was obtainable, together with glyoxylic acid, from the reaction of nitric acid with alcohol at ordinary temperature. When ammonia was allowed to react with glyoxal at 60 to 70°, the products were glycosin, $C_6H_6N_4$, which separated directly, and a sirupy residue left after evaporation of the mother liquor. The sirup was mixed with a saturated solution of oxalic acid, whereupon a large quantity of beautiful crystals was obtained. The free base was recovered from the oxalate by precipitation of the calcium salt. He called the new compound glyoxaline, from the starting material. Not till 24 years later was its cyclic amidine structure determined[143] and then chiefly by analogy with lophine and amarine (see page 450). Because of the structural resemblance to oxazole and thiazole, the name imidazole was later proposed.

The original process produced imidazole according to the reaction shown below, in which the 2-aldehydo group probably is eliminated by aerial oxidation. The glyoxal may be replaced by glyoxal sulfate, which is prepared conveniently from acetylene tetrachloride, oleum, and mercuric sulfate.[144] The sulfate is then stirred with formaldehyde and



[140] Hayes and Hunter, *J. Chem. Soc.*, 1 (1941).

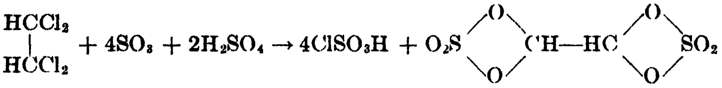
[141] Fowkes and McClelland, *ibid.*, 187 (1941).

[142] Debus, *Ann.*, **107**, 204 (1858).

[143] Japp and Robinson, *Ber.*, **15**, 1268 (1882); Radziszewsky, *ibid.*, **15**, 1493, 2706 (1882); Japp, *ibid.*, **15**, 2410 (1882); **16**, 284 (1883); Hantzsch, *Ann.*, **249**, 1 (1888).

[144] Ruggli and Henzi, *Helv. Chim. Acta*, **12**, 362 (1929).

ammonium hydroxide at a temperature below 55°. The solution may

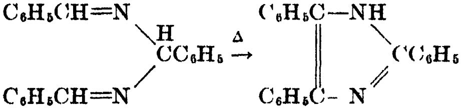


be used directly for many purposes that employ imidazole. The parent hydrocarbon can be prepared also by pyrolysis of 4,5-imidazole dicarboxylic acid in the presence of copper.[145]

Imidazole melts at 88 to 90° and boils at 262 to 264°. Like many of its derivatives, it has a marked physiological effect and increases the blood pressure because of vascular contraction.

4(5)-*Methylimidazole* can be obtained[146] in about 10 per cent yield by allowing dextrose to stand with zinc hydroxide in ammonia. *d*-Mannose, *d*-sorbose, *l*-arabinose, *l*-xylose, and lactose (to a smaller degree), but not sucrose, behave similarly. Rhamnose, however, produces imidazole, 4-methylimidazole, and 2,4-*dimethylimidazole*. *d*-Galactose yields a compound $C_{12}H_{39}O_{16}N_3Zn$.

Lophine.—Benzaldehyde and ammonia give hydrobenzamide; and this product, when heated above 360°, gives lophine[147] in about 40 per



cent yield. A nearly quantitative yield is obtained from an equimolecular mixture of benzil and benzaldehyde in boiling glacial acetic acid with ammonium acetate.[148] The condensation takes place also in alcoholic ammonia, but with lower yields.[149]

Lophine melts at 273°. Oxidation by chromic acid in dilute acetic acid gives dibenzamide and benzamide. Iodine in liquid ammonia converts it to cyaphenine (page 514), probably by way of a ring opening.[150]

Amarine is dihydrolophine. It is an intermediate in the preparation of lophine by pyrolysis of hydrobenzamide. The compound loses hydrogen very readily. Mild oxidizing agents,[151] such as iodine in liquid ammonia,[152] or potassium amide in liquid ammonia,[152] or heat, convert amarine to lophine. Reducing agents do not reverse the reaction.

---

[145] Snyder, Hendrick, and Brooks, *Org. Syntheses*, **22**, 65 (1942).

[146] Windaus and Knoop, *Ber.*, **38**, 1166 (1905); Windaus, *ibid.*, **40**, 799 (1907).

[147] Laurent, *Compt. rend.*, **19**, 353 (1844); *J. prakt. Chem.* [1], **35**, 455 (1845).

[148] Davidson, Weiss, and Felling, *J. Org. Chem.*, **2**, 319 (1937).

[149] Radziszewski, *Ber.*, **15**, 1493 (1882).

[150] Fischer and Trosche, *ibid.*, **13**, 706 (1880).

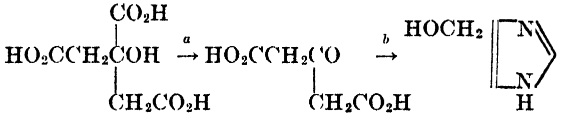
[151] Biltz and Krebs, *Ann.*, **391**, 213 (1912).

[152] Strain, *J. Am. Chem. Soc.*, **52**, 1218 (1930).

Amarine may be obtained by treating hydrobenzamide with potassium amide in liquid ammonia, or by condensing benzoin,[149] benzaldehyde, and ammonia together. The compound melts at 129° and forms a silver salt.[153]

4,5-*Diphenylimidazoles* and related compounds are made by methods similar to those for lophine. For example, benzil and formaldehyde (hexamethylenetetramine) condenses to 4,5-diphenylimidazole;[148] benzaldehyde, propaldehyde, and ammonium acetate in boiling glacial acetic acid yield 4,5-diphenyl-2-ethylimidazole[154] (m.p. 229°); isobutaldehyde, salicylaldehyde, and anisaldehyde in place of propaldehyde yield the corresponding 2-substituted 4,5-diphenylimidazole. Phenanthraquinone may be used in place of benzil.

4(*or* 5)-*Hydroxymethylimidazole* (m.p. 94°) is an important intermediate for the preparation of histamine or histidine. Formerly, it was prepared[155] from citric acid by the following steps:



[a] $H_2SO_4 \cdot SO_3$. Converts the α-hydroxy acid system to a carbonyl. The action is general for α-hydroxy acids. Compare with the reaction of malic acid on page 153.

[b] (1) HNO_2. Forms the dioxime, HON=CHC(O)CH=NOH. (2) $SnCl_2$. Reduces the dioxime to diaminoacetone. (3) KCNS. Causes condensation to a thioimidazole compound, H_2NCH_2—I—SH (I = imidazole nucleus). (4) HNO_3. Removes the mercapto groups by oxidation and converts the amine to a hydroxy group with the nitrous acid formed as a by-product in the reaction. The process gives $HOCH_2$—I—H.

More recently, the preparation has been made possible from fructose.[156] In ammoniacal cupric acetate solution fructose decomposes to 1 molecule of dihydroxyacetone and 1 of glycerol aldehyde.

$$C_6H_{12}O_6 \rightarrow HOCH_2C(O)CH_2OH + HOCH_2CH(OH)CHO$$

The former condenses with formaldehyde and ammonia in the presence of cupric salts to form the imidazole; the latter merely suffers further oxidation.

Imidazole-4(5)-*carboxylic acid* (m.p. 286 d.) is obtained by oxidation of 4(5)-hydroxymethylimidazole with nitric acid.[155]

β-(4-*Imidazolyl*)*propionic* acid is obtained from levulinic acid by bromination, subsequent treatment[157] of the dibromo product with boiling water, and condensation[158] of the resulting glyoxylpropionic acid with ammonia and formaldehyde. It may also be obtained from

---

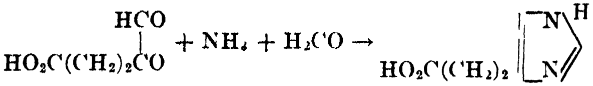
[153] Snape and Brooke, *J. Chem. Soc.*, **75**, 210 (1889).

[154] Cook and Jones, *ibid.*, 278 (1941).

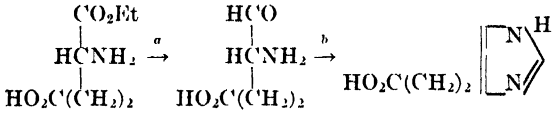
[155] Pyman, *ibid.*, **109**, 186 (1916); Koessler and Hanke, *J. Am. Chem. Soc.*, **40**, 1716 (1917).

[156] Weidenhagen, Hermann, and Wagner, *Ber.*, **70**, 570 (1937).

[157] Wolff, *Ann.*, **260**, 79 (1890).



glutamic acid[159] by reduction of the ester with sodium amalgam (a general reaction for formation of α-aminoaldehydes) and conversion of the amino aldehyde product to an imidazole derivative by thiocyanic acid. Ferric chloride oxidation completes the synthesis.[160] The acid is inter-



[a] NaHg. [b] KSCN, FeCl$_3$.

esting because of its relationship to histamine.

Histamine, or β-aminoethylimidazole, occurs widely in nature as one of the products of putrefactive bacteria on histidine.[161] It is found in aqueous extracts of ergot[162] along with putrescine, cadaverine, and the physiologically active β-hydroxyphenylethylamine. In the laboratory, it can be prepared from 4(5)-hydroxymethylimidazole by a series of reactions at the 4-hydroxymethylene end of the molecule. It may be

$$-CH_2OH \xrightarrow{a} -CH_2Cl \xrightarrow{b} -CH_2CN \xrightarrow{c} -CH_2CH_2NH_2$$

[a] PCl$_5$. [b] NaCN. [c] Na + alcohol

obtained also from imidazolylpropionic acid[163] by conversion of the acid to an amino group (see below), or from α,γ-diaminobutyric acid by reagents (EtOH + HCl, NaHg, HCNS, FeCl$_3$) already mentioned as

$$I(CH_2)_2C(O)OH \xrightarrow{a} I(CH_2)_2C(O)N_3 \xrightarrow{b} I(CH_2)_2NH_2$$

I = imidazloyl residue.
[a] EtOH + HCl, H$_2$NNH$_2$, HNO$_2$. [b] HCl.

used in the formation of imidazolylpropionic acid from ethyl glutamate. The α,γ-diaminobutyric acid, necessary for this synthesis, can be obtained[164] from glutamic acid by way of ethyl hydantoinpropionate, a compound that will be described later.

---

[158] Windaus and Vogt, *Ber.*, **40**, 3691 (1907).

[159] Fischer, *ibid.*, **41**, 1021 (1908).

[160] Akabori, *ibid.*, **66**, 15 (1933).

[161] Ackerman, *Z. physiol. Chem.*, **65**, 504 (1910).

[162] Barger and Dale, *J. Chem. Soc.*, **97**, 2592 (1910).

[163] Pyman, *ibid.*, **99**, 668 (1911); Koessler and Hanke, *J. Am. Chem. Soc.*, **40**, 1716 (1918).

[164] Akabori and Numano, *Bull. Chem. Soc. Japan*, **11**, 214 (1936); *C.A.*, **30**, 5986 (1936).

Histamine melts at 83 to 84° and boils at 209 to 210° at 18 mm.

Like most β-substituted-ethylamines, it is physiologically active. (Compare, for example, with adrenaline and with tyramine, which is *p*-hydroxy-phenylethylamine.) The variety of these effects in the case of histamine is unusually large.[123,165] There is scarcely a tissue that will not respond in some way. It is a powerful vasodilator, although accompanied by side reactions that preclude the possibility of its use. It is a gastric stimulant. It is used in ointments for treatment of rheumatism. Its liberation in the tissues is regarded as responsible for manifestations of allergy, urticaria, asthma, sneezing, etc. Large doses cause histamine shock and convulsions.

Histidine is the amino acid that corresponds to histamine. It is a decomposition product of proteins and is present in urea and in germinating plants. It is regarded as one of the essential amino acids.[165]

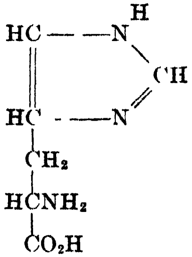
Synthesis[166] begins with 4 (or 5)-hydroxymethylimidazole. Oxidation by chromic acid converts the hydroxy to an aldehyde group. Condensation with hippuric acid and a sequence of steps as in the tryptophan synthesis (page 114) completes the formation.

$$ICH_2OH \xrightarrow{a} ICHO \xrightarrow{b} ICH_2CH(NH_2)CO_2H$$

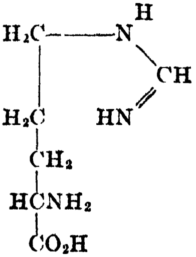
I = imidazole nucleus

[a] CrO_3. [b] Hippuric acid, Na_2CO_3, 2 per cent NaHg, 20 per cent HCl.

Histidine melts at 285 d.; the picrate melts at 234 to 235°. The compound is equivalent to argenine in metabolism; and the general similarity between these compounds played an important role in elucidating the structure.[167]



Histidine



Argenine

Histidine couples with diazonium salts to form azo dyes and is probably responsible for the ability of proteins in general to couple.[168] N-substituted histidine does not form azo dyes. The physiological effects, so marked in the case of histamine, are greatly reduced, if not absent, in histidine.

---

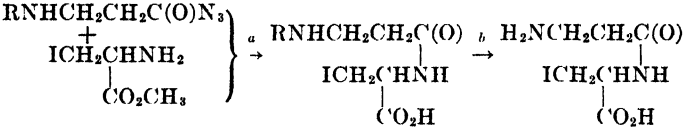
[165] Fox, *Chem. Rev.*, **32**, 47 (1943).

[166] Pyman, *J. Chem. Soc.*, **109**, 186 (1916); Koessler and Hanke, *J. Am. Chem. Soc.*, **40**, 1716 (1918).

[167] Pauly, *Z. physiol. Chem.*, **42**, 508 (1904).

[168] Burian, *Ber.*, **37**, 696 (1904).

Carnosine was first isolated from Liebig's beef extract and is the only β-amino acid known to exist in the body. The structure is shown[169] by hydrolysis with barium hydroxide to *l*-histidine and β-alanine and by synthesis. The best method of synthesis makes use of Bergmann's[170] excellent procedure for protecting the amino group with a carbobenzoxy radical, $C_6H_5CH_2OC(O)$—, while effecting condensation at the α-carbon atom in peptide synthesis. Carbobenzoxy-β-alanine[171] is converted by a series of conventional steps to the azide, the latter condensed with the ester of *l*-histidine, and the carbobenzoxy group eliminated by reductive hydrolysis.



$$\left.\begin{array}{l}\mathrm{RNHCH_2CH_2C(O)N_3}\\ \quad + \\ \mathrm{ICH_2CHNH_2}\\ \quad | \\ \quad \mathrm{CO_2CH_3}\end{array}\right\} \xrightarrow{a} \begin{array}{l}\mathrm{RNHCH_2CH_2C(O)}\\ \qquad\qquad\quad | \\ \mathrm{ICH_2CHNH}\\ \quad | \\ \quad \mathrm{CO_2H}\end{array} \xrightarrow{b} \begin{array}{l}\mathrm{H_2NCH_2CH_2C(O)}\\ \qquad\qquad\quad | \\ \mathrm{ICH_2CHNH}\\ \quad | \\ \quad \mathrm{CO_2H}\end{array}$$

R = Carbobenzoxy radical. I = Imidazole nucleus.

[a] This azide is derived from the corresponding acid by treatment with PCl_5, CH_3OH, H_2NNH_2, and HNO_2 in succession. The azide then reacts with the ester of *l*-histidine, and the resulting ester is saponified. [b] The carbobenzoxy radical is removed by aqueous sulfuric acid, hydrogen, and palladium.

The β-alanine used for the synthesis is obtained from succinimide by the Hofmann hypobromite method, and the carbobenzoxy radical is obtained from benzyl alcohol and phosgene. Carnosine melts at 206° d. in a capillary tube, and at 308 to 309° on a Dennis bar.

Anserine, $C_{10}H_{16}N_4O_3$, is monomethyl carnosine. It was first isolated from goose muscle and was purified[172] by means of the copper salt. The principal reactions[165] that have a bearing on the structure of this compound are (*a*) distillation with soda lime in a stream of hydrogen gives 1,5-dimethylimidazole; (*b*) the Pauly[173] diazo color test (formation of a dark cherry red color when treated with a freshly prepared solution of sodium diazobenzenesulfonate from sulfanilic acid and sodium nitrite) for an imidazole nucleus fails, and this coupling fails when the hydrogen attached to the imidazole nitrogen atom is replaced by a methyl group; (*c*) hydrolysis with barium chloride solution gives *d,l*-methylhistidine, separated as the phosphotungstate, and β-aminopropionic acid;[174] and (*d*) condensation of the peptide with dinitrotoluene and hydrolysis of the products with dilute sulfuric acid gives β-dinitrotoluylalanine rather than dinitromethylhistidine,[169] a fact which shows that methylhistidine is attached to β-aminopropionic acid (alanine) through the amino group of the former and the carboxyl group of the latter.

---

[169] Baumann and Ingvaldsen, *J. Biol. Chem.*, **35**, 263 (1918)· Barger and Tutin, *Biochem. J.*, **12**, 402 (1918).

[170] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

[171] Sifford and duVigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

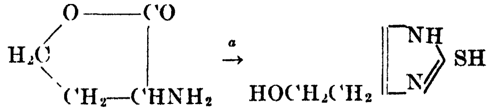
[172] Ackermann, Timpe, and Poller, *Z. physiol. Chem.*, **183**, 1 (1929).

[173] Pauly, *ibid.*, **44**, 159 (1905).

[174] Pymen, *J. Chem. Soc.*, 183 (1930).

Associated with these decisive tests are such confirmatory reactions as the presence of a primary amino group as tested by nitrous acid, the absence of unsaturation ($KMnO_4$), and the absence of positive clues from oxidations by chromic acid, nitric acid, and hydrogen peroxide and from reduction by hydriodic acid.

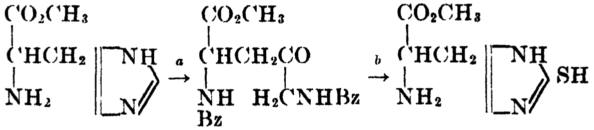
Histidol (m.p. 92°) is 4- (or 5)(β-hydroxyethyl)imidazole. It was discovered by Ehrlich[175] in the product of yeast fermentation of histidine and can be prepared[176] by reduction of α-aminobutyrolactone hydrobromide with 3 per cent sodium amalgam below −10°, followed by condensation with ammonium thiocyanate. The compound can be converted smoothly to histamine by phosphorus pentachloride followed by



a NaHg, HCNS.

alcoholic ammonia under pressure and heat.

2-Thiolhistidine and 2-Thiolhistamine.—The synthesis of the methyl ester of 2-thiolhistidine from the methyl ester of histidine provides an excellent example of the breakdown of the imidazole nucleus and reassembly with the appropriate reagents[177]



a C_6H_5COCl + Na_2CO_3 in order to form a tribenzoyl derivative, CH_3OH + HCl in order to eliminate one benzoyl group and give the ketone. b 20 per cent HCl, NaSCN.

A similar series of reactions can be used for preparing the analogous histamine compounds. In general, the thiol group reduces or eliminates the physiological activity.

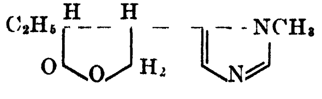
Pilocarpine, $C_{11}H_{14}O_2N_2$, is the chief alkaloid in the South American shrub known as *Pilocarpus jaborandi* and *P. microphyllus*.[123] The natives chew it to cause salivation. It also causes sweating, and, when applied locally to the eye, miosis. It is used in medicine as a diaphoretic. Pilocarpine and arecoline have somewhat similar physiological activity.

[175] Ehrlich, *Ber.*, **44**, 139 (1911).

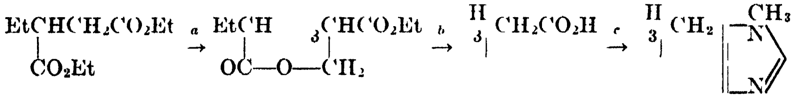
[176] Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

[177] Ashley and Harrington, *ibid.*, 2586 (1930); Pyman, *ibid.*, 98 (1930).

The structure,[178] shown below, for pilocarpine was deduced from the facts that (*a*) alkaline pyrolysis gives 1,5-dimethylimidazole and a methylamylimidazole; (*b*) heat converts the compound to the isomeric, isopilocarpine, which in turn is oxidized by permanganate to pilopic acid, $C_7H_{10}O_4$, a lactone, as shown by titration; (*c*) oxidation of pilopic acid gives butyric acid.



Synthesis[179] begins with a derivative of succinic acid, progresses by conventional steps to (*a*) pilopic acid, (*b*) homopilopic acid, and thence to (*c*) a mixture of the stereoisomeric compounds pilocarpine and isopilocarpine, which is separated by use of the strychnine salt.



Pilopic acid Homopilopic acid

[a] $HCO_2Et + NaOEt$, AlHg, distillation and loss of EtOH.

[b] HCl, PCl_5, CH_2N_2, Ag_2O, H_2O

[c] $SOCl_2$, CH_2N_2 (the chloromethyl ketone is formed instead of the diazo ketone), phthalimide, $H_2O{\cdot}HCl$, HSCN, $FeCl_3$, CH_3I.

The conversion of homopilopic acid to pilocarpine may be accomplished by the alternative route[180] shown below.

$$RCH_2CO_2H \xrightarrow{a} RCH_2C(O)CH{=}CHC_6H_5 \xrightarrow{b} \text{pilo- and isopilo-carpine}$$

R = substituted heterocyclic system, $C_6H_9O_2$

[a] $SOCl_2$, CH_3ZnI, C_6H_5CHO. [b] O_3, $NH_3 + H_2CO$, CH_3I.

Pilocarpidine, $C_{10}H_{12}O_2N_2$, is the methyl-free imino compound corresponding to pilocarpine. It is found in nature associated with the other alkaloids in *P. microphyllus.* Its synthesis in the laboratory is, of course, the same as that for pilocarpine, save for the last step.

Pilosinine is the ethyl-free compound corresponding to pilocarpine. It is prepared from ethyl succinate by steps essentially the same as those used for pilocarpine.[181]

Biotin is 2′-keto-3,4-imidazolido-2-tetrahydrothiophene-*n*-valeric acid. It is the growth-promoting factor in yeast. It is present also in liver, kidney, and eggs, and to a less degree in milk. It was first isolated by Kögl[182] from egg yolk, in 1936, after an exhaustive series of separations. The structure[183a] is determined from the following facts: (*a*) A diamino-

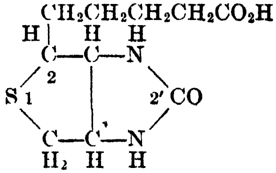
---

[178] Jowett, *ibid.*, **77**, 473, 493, 851 (1900); **79**, 580, 1331 (1901); **83**, 438, 464 (1903).

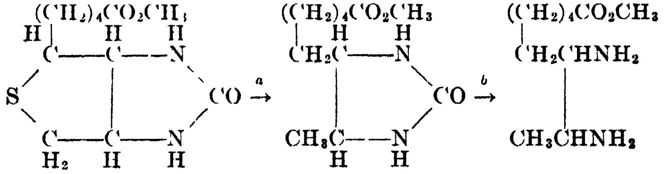
[179] Preobrashenski, Wompe, and Preobrashenski, *Ber.*, **66**, 1187 (1933); Chitchibabin, Wompe, and Preobrashenski, *ibid.*, **63**, 460 (1930).

[180] Dey, *J. Chem. Soc.*, 1057 (1937).

[181] Polyakova, Preobrashenski, and Preobrashenski, *J. Gen. Chem.*, *U.S.S.R.*, **9**, 1402 (1939); *C.A.*, **34**, 1658 (1940).



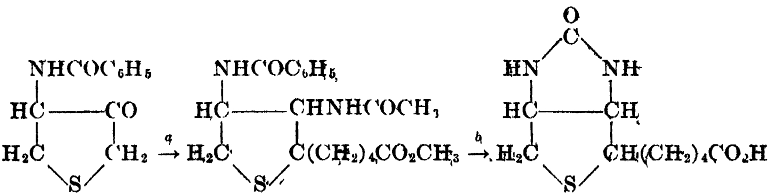
carboxylic acid is obtained from biotin and barium hydroxide at 140°. Biotin is reformed when this acid reacts with phosgene. (*b*) Double bonds are absent. (*c*) Nitric acid or permanganate oxidizes biotin to adipic acid. (*d*) The carboxyl group can be esterified and then converted to an amino group by a Curtius degradation. Oxidation of this amino product yields no adipic acid. (*e*) A Hofmann degradation, of the diaminocarboxylic acid, gives a thiophene valeric acid. (*f*) The sulfur can be eliminated from the methyl ester of biotin by Raney nickel. The desthiobiotin so obtained hydrolyzes to desthiodiamino carboxylic acid, which in turn with periodate gives pimelic acid and with phenanthraquinone gives a quinoxaline. Steps to the diamino compound are shown below.



[a] Ni. [b] Ba(OH)$_2$.

The identity of the desthiodiaminocarboxylic acid can be proved by synthesis from ethyl acetoacetate.

Synthesis[183b] of *d,l*-biotin is accomplished by the plan shown below.



The starting material is 4-benzamido-3-ketotetrahydrothiophene, which is prepared by a sequence of reactions that begins with the reaction of *l*-cysteine, $H_2NCH(CO_2H)CH_2SH$, and chloroacetic acid in alkaline solution to give β-(carboxymethylmercapto)-alanine, $NH_2CH(CO_2H)CH_2SCH_2CO_2H$, and is followed by successive reactions with benzoyl chloride and with methyl alcohol and sulfuric acid that give the N-benzoyl and methyl ester. Ring closure with sodium methoxide and heating of the ester in HCl-aq. HOAc at 135 to 140°, to effect hydrolysis and decarboxylation, completes the preparation of the starting material.

---

[182] Kögl and Tönnis, *Z. physiol. Chem.*, **242**, 43 (1936).

[183a] duVigneaud, Hofmann, and Melville, *J. Biol. Chem.*, **140**, 643 (1941); duVigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy, and Harris, *ibid.*, **146**, 475 (1942).

[183b] Harris, Wolf, Mozingo, Arth, Anderson, Easton, and Folkers, *J. Am.*

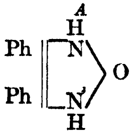
[a] The thiophene compound condenses (in acetic acid with piperidine as a catalyst) at its active methylene group with the aldehyde function of γ-formylbutyrate, $OCH(CH_2)_3CO_2CH_3$, itself prepared from glutaric anhydride by successive reactions with methyl alcohol to form the half ester, thionyl chloride to form the acid chloride, and hydrogen over palladium-barium sulfate to form the aldehyde. The product is an unsaturated keto ester, which is treated with hydroxylamine in pyridine solution to form the oxime. The oxime and olefin bond are then simultaneously reduced with zinc and acetic acid-acetic anhydride mixture.

[b] Hydrolysis with $Ba(OH)_2$ at 140° eliminates the benzoyl group, the acetyl group, and the alcohol of the carbomethoxy group. Reaction of the diamino acid product with phosgene in aqueous sodium carbonate below 10° gives *d,l*-biotin. Resolution is effected by means of the mandelic acid ester.

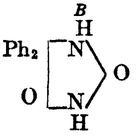
Biotin melts at 230 to 231°. It is identical with vitamin H and with coenzyme R.

Imidazolones.—Many of these compounds form readily by condensations that utilize urea or like reagents. For example, benzoin and urea in acetic acid give 4,5-diphenyl-3-imidazolone[184] (*A*); benzil, alcoholic potassium hydroxide and urea give diphenylhydantoin[185] (*B*); and benzil and urea give diphenylacetylenediurein[186] (*C*). Similarly, dimethylketol and diacetyl yield 4,5-dimethyl-3-imidazolone[186] and dimethylacetylenediurein,[187] respectively. The parent acetylenediurein[186] is prepared, of course, from glyoxal. The methods of preparation are general ones, applicable to other keto alcohols or diketo compounds.

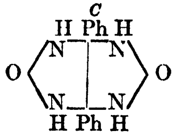
A



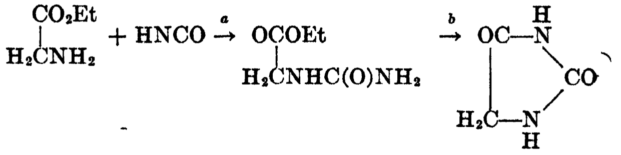
B



C



Hydantoin is prepared readily from the ethyl ester of glycine by condensation with potassium cyanate and ring closure of the product, ethyl hydantoate, with acid.



[a] HCl. [b] 20 per cent HCl.

Chem. Soc., **67**, 2096 (1945); WOLF, MOZINGO, HARRIS, ANDERSON, and FOLKERS, *ibid.*, 2100.

[184] ANSCHÜTZ and GELDERMAN, *Ann.*, **261**, 129 (1891).

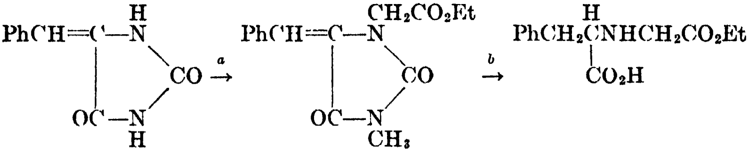
[185] BILTZ and RIMPEL, *Ber.*, **41**, 1379 (1908).

[186] BILTZ, *ibid.*, **40**, 4799, 4806 (1907).

[187] FRANCHIMONT and KLOBBIE, *Rec. trav. chim.*, **7**, 236 (1888).

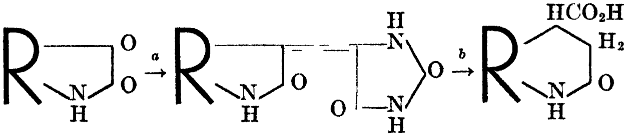
The ring is opened to form hydantoic acid by barium hydroxide (a common reagent when urea is in a nucleus). Bromine introduces two bromine atoms at the active methylene group. Nitric acid nitrates one of the nitrogen atoms to give an N-nitro compound.[188]

Benzaldehyde, and other aldehydes, condense readily with hydantoin. Since the ring system is readily opened, this reaction can be used in the same manner as hippuric acid or rhodanine to obtain open-chain compounds with specific groups.[189] For example, the condensation with benzaldehyde is the first step to the ester of β-phenylalanine N-acetic acid as shown below.



ᵃ CH_3I, NaOEt, $ClCH_2CO_2Et$. ᵇ HI + P, $Ba(OH)_2$.

Hydantoin can also be used in the preparation[190] of quinoline compounds by reaction with isatin as shown below.



ᵃ Condensation with hydantoin under the influence of fused NaOAc in glacial HOAc at 150° for 3 hr. ᵇ Sn + HCl, $Ba(OH)_2$.

5-Substituted hydantoins can be prepared by methods analogous to those used for hydantoin itself.[191]

α-Amino acids, of which a large number exist from the decomposition of proteins, react with potassium cyanate, and the uramido acid product, in turn, suffers ring closure when boiled with dilute mineral acid, usually 10 per cent hydrochloric. Glutamic acid thus yields hydantoinpropionic acid. The process is essentially the same as that already pictured for the preparation of hydantoin from glycine.

Hydantoins may also be prepared from malonamides[192] or from ketones,[193] as illustrated by the equations below.

[188] BAILEY, *Am. Chem. J.*, **28**, 386 (1902); HARRIES, *Ann.*, **361**, 71 (1908).

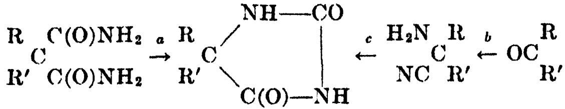
[189] LITZINGER, *J. Am. Chem. Soc.*, **56**, 673 (1934).

[190] HILL and HENZE, *ibid.*, **46**, 2806 (1924); HILL, SCHULTZE, and LINDWALL, *ibid.*, **52**, 769 (1930).

[191] DAKIN, *Am. Chem. J.*, **44**, 48 (1910).

[192] READ, *J. Am. Chem. Soc.*, **44**, 1746 (1922).

[193] BILTZ and SLOTTA, *J. prakt. Chem.*, **113**, 233 (1926); HERBST and JOHNSON, *J. Am. Chem. Soc.*, **54**, 2463 (1932).



[a] KOCl converts one of the amide groups to an isocyanate, HX then effects ring closure. [b] NH_4CN.
[c] KOCN yields a mono-substituted urea by reaction with the amino group, HX causes hydrolysis and ring closure.

This last reaction has wide applicability. Twenty-four common aldehydes (formaldehyde excepted), 36 ketones, and at least 50 carbonyl compounds condense in this manner.[194]

Some 5-disubstituted hydantoins act as hypnotics. They have a structure similar to the barbiturates and conform to the general rule[195] that hypnotic compounds almost invariably consist of lipo-soluble alkyl radicals attached to water-soluble or polar groups, which are capable of forming associated molecules in aqueous solvents and which may or may not possess similarity to structures occurring in the body. They are stable enough to prevent too rapid destruction in the body before they exert their effect; yet they suffer a necessary degree of degradation. The acidity or basicity is not pronounced. The total number of carbon atoms in the alkyl groups should be about 10 or 11 for best results.[196]

Nirvanol, 5,5-ethylphenylhydantoin, is a practical example of such hydantoin derivatives.[197] It is of some value in the treatment of chorea and other nervous disorders. Its continued use as a hypnotic leads to fever and skin eruptions.[123]

Allantoin is widely distributed in nature, particularly in the embryo of plants and animals. Its name indicates its presence in the allantois of the cow. Germinating plants, mushrooms, cauliflower leaves, soybeans, liver, and urine contain it.[198] The *d*-form can be isolated from leaves by extraction with water, followed by a series of purifications that includes precipitation with basic lead acetate, recovery with hydrogen sulfide, elimination of the sulfide, double precipitation with sodium mercuric acetate (Wiechowskii's reagent), recovery with hydrogen sulfide again, etc. The *l*-form can be obtained from soybeans by action of the enzyme allantoinase, which converts the *d*-form to allantoic acid but leaves the *l*-form unchanged.

In the laboratory, it is prepared in 64 to 76 per cent yield by oxidation of uric acid[199] with potassium permanganate. The double bond is first oxidized, a rearrangement effected, and carbon dioxide lost on acidification. It may also be prepared by heating glyoxylic acid with urea.

---

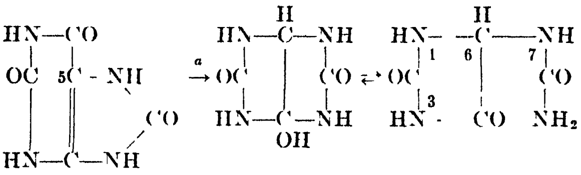
[194] Henze and Speer, *ibid.*, **64**, 522 (1942); Henze, Thompson, and Speer, *J. Org. Chem.*, **8**, 17 (1943).

[195] Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

[196] Dox, *J. Am. Pharm. Assoc.*, **12**, 602 (1923).

[197] Rigler and Henze, *J. Am. Chem. Soc.*, **58**, 474 (1936).

[198] Fosse, Thomas, and de Graeve, *Compt. rend.*, **198**, 1374, 1953 (1934); *C.A.*, **28**, 4384, 5496 (1934).

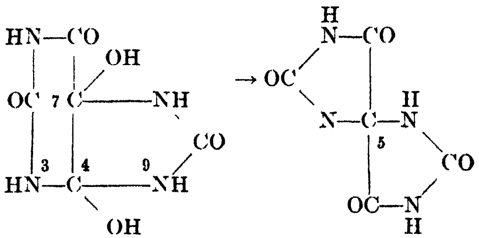


^{a} $KMnO_4$ + H_2O, HX.

Allantoin is weakly acidic. It forms a silver salt with ammoniacal silver nitrate and a potassium salt with cold concentrated potassium hydroxide. After many hours standing, alkali converts it to allantoic acid, $H_2NC(O)NHCH_2NHC(O)NHCO_2H$. Reduction with hydriodic acid gives hydantoin. Xanhydrol and methylxanhydrol give a precipitate of allantoic acid that is useful in analysis.[200]

Allantoin stimulates tissue growth and promotes healing of wounds. During the First World War, and even earlier, wounds infested with maggots were observed to heal faster than wounds not so infested. The explanation of this seeming anomaly came after an examination of the drainings recovered by atomizing water over several thousand maggots (contained in a funnel half-filled with glass balls to prevent crushing the insects) and by the discovery of allantoin therein. Maggots, therefore, perform the dual role of consuming necrotic tissue and bacteria and of excreting allantoin that stimulates growth of fresh tissue. The process has met with peacetime use,[201] particularly in the treatment of deep-seated infections not reached by application of solutions of allantoin.

Spirohydantoin is obtained from 4,5-dihydroxy-4,5-dihydrouric acid by treatment with concentrated sulfuric acid on a water bath.[202] The change is of the pinacolin rearrangement type.



---

[199] HARTMAN, MOFFETT, and DICKEY, *Org. Syntheses*, **13**, 1 (1933).

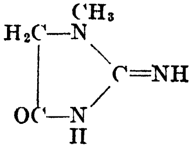
[200] FOSSE, BRUNEL, and DE GRAEVE, *Compt. rend.* **188**, 1418 (1929); *C.A.*, **23**, 4495 (1929); FOSSE and BRUNEL, *Compt. rend.*, **197**, 288 (1933); *C.A.*, **27**, 5376 (1933).

[201] ROBINSON, *J. Parasitol.*, **21**, 354 (1935); *C.A.*, **30**, 3090 (1936).

[202] BILTZ, HUYN, and BERGIUS, *Ann.*, **413**, 77 (1917); POPE and WHITWORTH, *J. Chem. and Ind.*, **49**, 748 (1930).

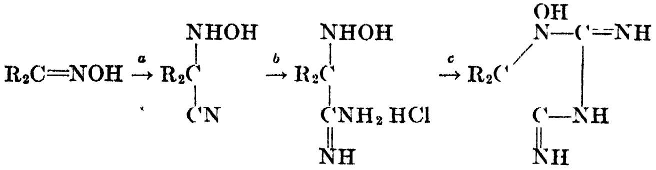
Parabanic acid is triketoimidazole. It can be obtained by hydrolysis of the dibromide of hydantoin. It is also formed by oxidation of uric acid with warm nitric acid and by condensation of urea with oxalyl chloride. It melts at 242 to 244° and forms an insoluble silver salt.[203]

Creatinine was originally obtained from urine, but can be better derived from creatine, $C_4H_9N_3O_2$, a product obtainable in considerable quantity from animal tissue.[204]



Evaporation of a solution of creatine in 6 *N* hydrochloric acid gives the crystalline creatinine hydrochloride.[205] The free base is recovered by treatment with ammonia. Creatinine has an active methylene group that condenses with aldehydes.[206]

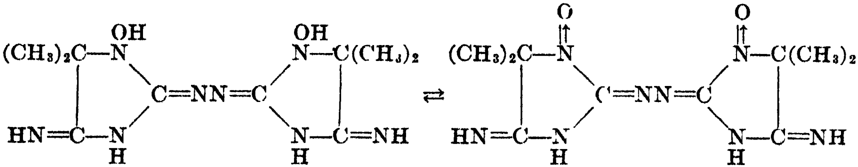
Porphyrexin is produced from acetoxime by a series of reactions that includes the addition of hydrogen cyanide to a C=N double bond, the familiar formation of an amidine, and ring closure.[207]



a HCN. b HCl + HOEt, NH_3. c HCN. R = CH_3.

Porphyrexide is the oxidized (N-oxide) or red form derived from the colorless porphyrexin.

Porphyrindin.—The reaction of porphyrexin with hydrazine gives leuco-porphyrindin, which is convertible to a blue product, porphyrindin, by oxidation.



Leucoporphyrindin Porphyrindin

---

[203] Wood, *J. Chem. Soc.*, **89**, 1834 (1906); Biltz and Topp, *Ber.*, **46**, 1387 (1913).

[204] Folin and Denis, *J. Biol. Chem.*, **8**, 399 (1910); Benedict, *ibid.*, **18**, 183 (1914).

[205] Edgar and Hinegardner, *ibid.*, **56**, 881 (1923).

[206] Cornthwaithe, Lazarus, Snelling, and Denoon, *J. Am. Chem. Soc.*, **58**, 628 (1936).

[207] Lillevik, Hossfeld, Lindstrom, Arnold, and Gortner, *J. Org. Chem.*, **7**, 164 (1942).

Porphyrindin, a powerful oxidizing agent, reacts rapidly and stoichiometrically with cysteine and with protein —SH groups in the cold. The dye is deep blue in the oxidized and slightly yellow in the reduced state. At pH 7.0, $E_0 = +0.57$ volts.

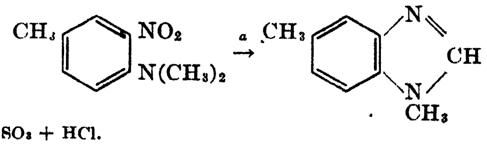
Porphyrindin is useful for estimating protein sulfhydryl groups,[208,209] which in turn play an important part in cellular respiration and enhance the functioning of certain hydrolytic biocatalysts such as urease, papain, kathepsin, and cerebrosidase. The appearance of a free sulfhydryl group coincides also with loss in activity of such active principles as insulin.

Porphyrexide and prophyrindin can be reduced to their colorless leuco form by pyrrocatechol, hydroquinone, pyrogallol, cystein, and ascorbic acid. The reduction can be followed potentiometrically in an atmosphere of pure nitrogen. The form of the titration curve is in good agreement with that predicted for free radicals.[210]

Benzimidazole is prepared from *o*-phenylenediamine by reaction with formic acid, or compounds, such as chloroform and alkali or hydrogen cyanide, that are capable of forming formic acid.[211] The compound melts at 170° and boils above 360°. It forms a 1-methyl derivative with methyl iodide at 240° or with potassium methyl sulfate.

Benzimidazole silver is insoluble in ammonia solution,[212] possibly because the silver salt exists as an inner complex in which the partial valence of the nitrogen atom in the ring, rather than the nitrogen in the ammonia molecule, is attached to the silver. Copper forms a brick-red complex[213] when an ammoniacal cupric acetate solution and benzimidazole react together. The complex is stable to boiling potassium hydroxide (4 *N*) but unstable to ammonium sulfide or potassium cyanide. Its formation can serve as a test, either for small quantities of copper or of imidazole. Nickel forms an ultramarine blue complex, cobalt yields a similar but reddish one, and cadmium and zinc form white products.

1,5-*Dimethylimidazole* is obtained by reduction of 3-nitro-4-dimethylaminotoluene.[214] Intermediate nitroso groups are formed in the process.



[a] Sn + HCl or $NaHSO_3$ + HCl.

[208] Kuhn and Desnuelle, *Z. physiol. Chem.*, **251**, 14 (1938).

[209] Greenstein, *J. Biol. Chem.*, **125**, 501 (1938); Grunstein and Jenrette, *ibid.*, **142**, 175 (1942).

[210] Kuhn and Franke, *Ber.*, **68**, 1528 (1935).

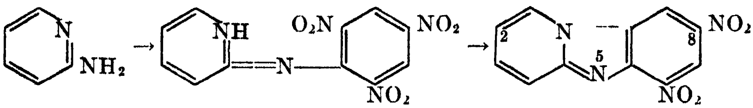
[211] Wundt, *ibid.*, **11**, 826 (1878); Dains, *ibid.*, **35**, 2503 (1902).

[212] Bamberger and Lorenzen, *Ann.*, **273**, 279 (1893).

[213] Skraup, *ibid.*, **419**, 1 (1919).

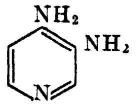
[214] Pinnow, *Ber.*, **28**, 3041 (1895); *J. prakt. Chem.*, **65**, 579 (1902); Lauer, Sprung, and Langkammerer, *J. Am. Chem. Soc.*, **58**, 225 (1936).

Pyridobenzimidazole is an example of the complex systems that can be prepared.[215] 2-Aminopyridine reacts with picryl chloride. The N-2′,4′,6′-trinitrophenyl-2-aminopyridine so produced loses nitrous acid readily when heated in boiling dimethylaniline. The product is pyrido[1,2-*a*]-6,8-dinitrobenzimidazole, also called 1,2-pyrido-7,9-dinitro-4,5-benz-1,3-diazoline.

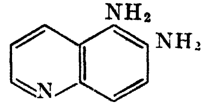


The structure is proved by reduction (platinum and hydrogen) of the two nitro groups and then removal of the amino groups by boiling the tetrazotate in alcohol to obtain the known parent compound (m.p. 179°). Similar compounds can be prepared from the amino derivative of quinoline, isoquinoline, and phenanthridine.

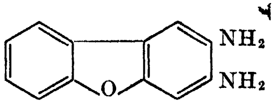
The compounds below are all convertible to imidazoles by reaction with an aldehyde in the presence of ammoniacal cupric acetate.[216] The products obtained with formaldehyde are, respectively, 1-imidazole[*c*]pyridine, 1-imidazole[*f*]quinoline, and 3-benzofuro[2,3-*f*]benzimidazole otherwise known as imidazolo-5′,4′,2,3-diphenylene oxide.



(From γ-pyridone nitrate by nitration, chlorination with phosphorus penta- and oxychlorides, treatment with methanol to give the methoxy compound, ammonolysis with ammonia under pressure, reduction of nitro group)



(From 6-aminoquinoline by nitration and reduction)



(From diphenylene oxide by nitration reduction, nitration, and reduction)

MISCELLANEOUS AZOLES

The oxadiazoles, thiadiazoles, triazoles, and tetrazoles are not, in general, so important as the other azole compounds with fewer hetero atoms. The general chemistry of these compounds has been described in the previous chapter. A limited number of compounds will be described here.

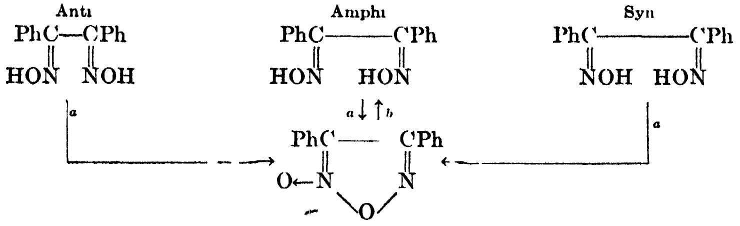
Furoxans have an interesting relationship to the anti, syn, and amphi dioximes.[217] Reduction opens the ring and gives the amphi dioxime only. Oxidation of the *anti*, *amphi*, or *syn* dioxime gives only the one furoxan. The illustration below is typical of the results obtained when the groups attached to carbon are the same. More complicated systems are encountered when the groups are different.

---

[215] Morgan and Stewart, *J. Chem. Soc.*, 1292 (1938).

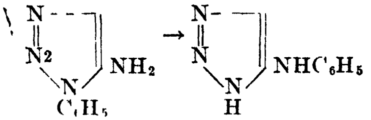
[216] Weidenhagen and Weeden, *Ber*, **71**, 2347 (1938).

[217] Wieland and Semper, *Ann.*, **358**, 36 (1908); Meisenheimer and coworkers, *ibid*, **444**, 94 (1925); **468**, 202 (1929); Kinney, *J. Am Chem. Soc.*, **51**, 1592 (1929).

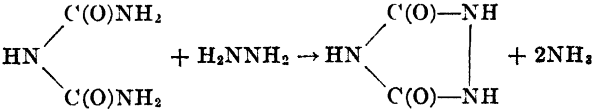


[a] Oxidation with sodium hypochlorite. [b] Reduction with zinc dust and acetic acid in alcohol

1-*Phenyl*-5-*amino*-1,2,3-*triazole* (m.p. 110°) is prepared from 1-phenyl-1,2,3-triazole-5-carboxylic acid by a Curtius reaction. The amino group can be diazotized and the diazo compound coupled with β-naphthol. The amino compound undergoes an interesting isomerization at 145°, in boiling pyridine, or in hot acetic anhydride.[218] The product is the 5-anilino-1-phenyltriazole, as if the phenyl group had wandered from a nitrogen atom in the ring to one in the side chain. The mechanism is possibly a cleavage between the 1- and 2-positions with an interchange of nitrogen atoms between the ring and the amino substitutent.



Urazole (m.p. 244°) is obtained by heating urea with hydrazine.[219] The reaction proceeds through the intermediate formation of biuret.



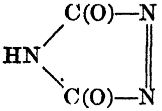
The compound dissolves easily in water, less readily in alcohol, and with difficulty in ether. It is acidic and forms a crystalline sodium salt. Phosphorus pentasulfide converts it to 1,2,4-triazole. Hot acetic anhydride and sodium acetate cleave the ring and form tetraacetylhydrazine. Oxidizing agents convert it to a cyclic azo compound,[220] known com-

---

[218] Dimroth, *Ber.*, **35**, 1029 (1902); *Ann.*, **262**, 272, 314 (1890).

[219] Pellezzari and Cuneo, *Gazz. chim. ital.*, **24**, I, 499 (1894); Thiele and Uhlfelder, *Ann.*, **303**, 94, 102 (1898); Diels, *Ber.*, **36**, 739, 744 (1903); Stollé and Krauch, *J. prakt. Chem.* [2], **88**, 313 (1913).

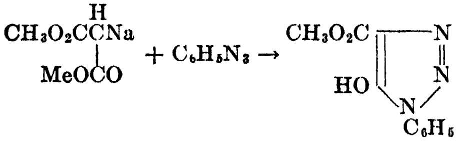
[220] Busch and Ulner, *Ber.*, **35**, 1718 (1902); Stollé, *ibid.*, **45**, 275, 286 (1912); Thiele and Stange, *Ann.*, **283**, 42 (1894).



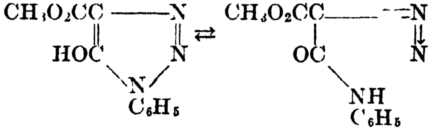
monly as azodicarbimid, but which might also be called dehydrourazole or 3,4-diketotriazoline. The silver salt of the azo compound and iodine give an unstable violet-colored oil that hydrolyzes readily and forms some urazole together with carbon dioxide, ammonia, and nitrogen.

Phenyl- and tolyl-urazole are prepared by methods analogous to those for urazole, but with phenylhydrazine and phenylsemicarbazide or the corresponding homologues instead of hydrazine.

1-*Phenyl*-4-*carbomethoxy*-5-*hydroxy*-1,2,3-*triazole* is prepared from the reaction of phenylazide and dimethyl sodiomalonate in methanol.



Compounds of this type were studied extensively by Dimroth,[221] who found that the equilibrium point between the triazole or enol form and the diazomalonanilide ester or keto form was dependent on the relative solubility of each form in the solvent employed.



1,2,5-*Triphenyl*-1,3,4-*triazole* is prepared from dibenzoylhydrazine and benzanilide or aniline at 240°. It possesses physiological properties not unlike those of strychnine. Similar methods of synthesis, applied to α-benzoyl-β-phenylacetylhydrazine yield the corresponding diphenylbenzyl compound.[222]

2-Phenyl-5-methyltetrazole[223] (m.p. 40°, b.p. 140°/15 mm.), has the odor of jasmine, although the isomeric 1-phenyl-5-methyl compound has no odor.

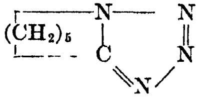
Metrazole, or pentamethylenetetrazole, is prepared from cyclohexanone by use of hydrazoic acid and sulfuric acid as described before (see page 372). The compound has a medicinal value[123] in the shock treatment of schizophrenia. The danger of bone breaking by metrazole shock during treatment is relieved by curare.

---

[221] Dimroth, *Ber.*, **35**, 4041 (1902); *Ann.*, **399**, 91 (1913); Dimroth and Taub, *Ber.*, **39**, 3915 (1906); Dimroth and Aikelin, *ibid.*, **39**, 4390 (1906).

[222] Bhagat and Rey, *J. Chem. Soc.*, 2357 (1930).

[223] Dimroth and Merzbacher, *Ber.*, **43**, 2899 (1910).



Problems

1. Name the products obtained in the following reactions: (*a*) Aminoacetone hydrochloride heated 1 min. with sodium acetate and acetic anhydride and the unpurified product warmed with phosphorus pentachloride or phosphorus pentasulfide on a water bath.[3] (*b*) Hydrazoic acid and phenylpropiolic acid.[224] (*c*) 3-Nitro-4-thiocyanoanisole (how prepared?) treated with concentrated hydrochloric acid and stannous chloride.[225] (*d*) *o*-Aminophenol heated with *p*-tolylnitrile.[226] (*e*) *o*-Aminophenol heated with hexahydrobenzamide.[226] (*f*) Furfural, warmed at 60° in an alcoholic solution of potassium cyanide and ammonium carbonate.[227] (*g*) Diethyl dipropylmalonate treated with phenylhydrazine in the presence of sodium ethoxide.[228] (*h*) Chloromalondialdehyde (how obtained?) allowed to react in alcohol solution with phenylhydrazine.[229] (*i*) α-Methylaminopropionacetal heated for 1 hr. on a water bath with potassium thiocyanate and hydrochloric acid.[230] (*j*) A methanol solution of furoin refluxed with copper acetate, formalin, and aqueous ammonia.[156] (*k*) α,α'-Dichloroacetone and thioacetamide allowed to stand together in a minimum volume of acetone.[231] (*l*) *p*-Chlorophenacyl bromide refluxed in alcohol with thioacetamide.[232] (*m*) Leucine treated with potassium cyanate and the product boiled with 10 per cent hydrochloric acid.[233] (*n*) Butyroin and urea.[234] (*o*) Thiourea and dichloroethyl ether in alcoholic solution.[235a] (*p*) Diethyl ketone treated with ethyl formate and sodium ethoxide and the product then treated with phenylhydrazine.[235b] (*q*) *o*-Phenylenediamine boiled for 30 min. with glycolic acid and 4N hydrochloric acid.[235c] (*r*) 4-Nitrodiacetyl-*o*-phenylenediamine hydrolyzed with aqueous hydrochloric acid.[235d] (*s*) Thioglycolic acid and methyl isothiocyanate.[235e] (*t*) Tetraacetylhydrazine heated with zinc chloride.[235f] (*u*) *p*-Ethoxyphenylthiourea allowed to react with thionyl chloride.[235g] (*v*) Bis[trichloroacetyl]hydrazine heated with phosphorus pentachloride at 150 to 160° or with thionyl chloride.[235h]

[224] Oliveri-Mendala and Coppola, *Gazz chim. ital.*, **40,** II, 440 (1910); Dimroth and Fester, *Ber.*, **43,** 2219 (1910).

[225] Ochiai and Katada, *J. Pharm. Soc. Japan*, **60,** 543 (1940); *C.A.*, **35,** 1785 (1941).

[226] (*a*) Wheeler, *Am. Chem. J.*, **17,** 399 (1895); (*b*) Skraup, *Ann.*, **419,** 1 (1919).

[227] Henze and Speer, *J. Am. Chem. Soc.*, **64,** 522 (1942); Henze, Thompson, and Speer, *J. Org. Chem.*, **8,** 17 (1943).

[228] Conrad and Zast, *Ber.*, **39,** 2282 (1906).

[229] Dieckmann and Platz, *ibid.*, **27,** 4644 (1904).

[230] Bartles, Pyman, and Roylance, *J. Chem. Soc.*, **127,** 581 (1930).

[231] Hooper and Johnson, *J. Am. Chem. Soc.*, **56,** 470 (1934).

[232] Wetherell and Hann, *ibid.*, **56,** 970 (1934).

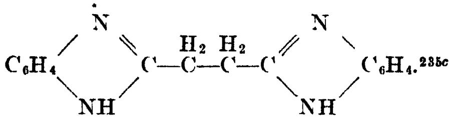
[233] Dakin, *Am. Chem. J.*, **44,** 48 (1910).

[234] Basse and Klinger, *Ber.*, **31,** 1217 (1898).

[235] (*a*) Schatzmann, *Ann.*, **261,** 1 (1891); (*b*) Claisen and Meyerowitz, *Ber.*, **22,** 3273 (1889); (*c*) Phillips, *J. Chem. Soc.*, 2393 (1928); (*d*) Phillips, *ibid.*, 172 (1928). (*e*) Andreash and Zipser, *Monatsh.*, **25,** 159 (1904); (*f*) Stollé, *Ber.*, **32,** 797 (1899); (*g*) duPont Company, British patent 379, 341; *C.A.*, **26,** 5103 (1932); **27,** 3946 (1933); (*h*) Stollé and Helwerth, *J. prakt. Chem.* [2], **88,** 315 (1913).

2. Devise a method for the preparation of the following compounds from readily available nonheterocyclic reagents: (*a*) 2,5-Dimethylthiazole.[236] (*b*) 2-Chlorothiazole.[235a] (*c*) Diphenylpyrazole.[118] (*d*) 3,4-Diphenyl-5-*p*-bromophenylisoxazole.[237] (*e*) 3,5-Diaminopyrazole from a pyrazole compound.[238] (*f*) 1-Phenyltriazole.[24,239] (*g*) 5-Nitro-1-phenylbenzimidazole.[240] (*h*) 4,5,6,7-Tetrahydrobenzimidazole from cyclohexanone.[241] (*i*) 2-Mercapto-5-carbethoxy-4-methylimidazole.[242] (*j*) 2-Ethyl-4(*p*-bromophenyl)-thiazole.[232] (*k*) 2,5-Diphenyl-1(*p*-tolyl)-1,3,4-triazole.[243] (*l*) 2-Phenyl-5-veratryloxazole, $(CH_3O)_2C_6H_3—\overline{C{=}CH—N{=}C(C_6H_5)O}$.[244] (*m*) 2-Phenyl-5-methyloxazole or the corresponding thiazole.[245]

3. Suggest a method for the preparation of each of the following heterocyclic compounds. The student should be able to write a total synthesis. (*a*) 5-Methylisoxazole.[246] (*b*) 3,4,5-Triethylpyrazole.[247] (*c*) 2,4-Dimethyl-5-phenylthiazole.[248] (*d*) 4-Isobutylimidazole from leucine.[249] (*e*) 3-Phenyl-5-mercapto-1,2,4-thiadiazole;[250] 3,5-diphenyl-1,2,4-selenadiazole.[251] (*f*) 5-Anilino-1,2,3-thiadiazole.[252] (*g*) 3,5-Diphenyl-2-trichloro-1,2-oxaphosphole.[253] (*h*) 2,5-Diphenylselenazole.[254] (*i*) 2-Phenyl-4-nitrobenzotriazole;[255] 1-phenyl-7-nitrobenzotriazole,[255] and 1-phenyl-5-nitrobenzotriazole.[256] (*j*) ββ'-Dibenzimidazolylmethane,



4. Name the product, or products, that may result from each of the following reactions or sequence of reactions: (*a*) Acetylpyruvic acid and the hydrochloride salt of phenylhydrazine in aqueous acid solution forms $C_{10}H_{10}N_2O_2$.[22] (*b*) 1-Alkyl-3-carbethoxy-4-piperidone hydrochloride heated with phenylhydrazine and one drop of hydrochloric acid in an oil bath at 110 to 150° gives $C_{12}H_{12}N_3O$.[257] (*c*) Cyanogen gas passed into a warm alcoholic solution of *o*-aminophenylmercaptan yields C_8H_7-

[236] Hubacher, *Ann.*, **259**, 228 (1890).
[237] Kohler and Richtmeyer, *J. Am. Chem. Soc.*, **50**, 3903 (1928).
[238] Knoor, *Ber.*, **37**, 3520 (1908).
[239] Michael, Luhn, and Higbee, *Am. Chem. J.*, **20**, 377 (1899).
[240] Phillips, *J. Chem. Soc.*, 2820 (1929).
[241] Weidenhagen and Wagner, *Ber.*, **71**, 2124 (1938).
[242] Ochiai and Ikuma, *ibid.*, **69**, 1147 (1936).
[243] Pellizzari and Alciatore, *Atti accad. Lincei*, **10**, I, 444 (1910).
[244] Robinson, *J. Chem. Soc.*, **95**, 2167 (1909).
[245] Gabriel, *Ber.*, **43**, 1283 (1910).
[246] Claisen, *ibid.*, **44**, 1161 (1911).
[247] Hahl, U.S. patent 1,879,210; *C.A.*, **27**, 1091 (1933).
[248] Bachstez, *Ber.*, **47**, 3163 (1914).
[249] Akabori and Numano, *ibid.*, **66**, 159 (1933).
[250] Crayen, *ibid.*, **24**, 385 (1891).
[251] Becker and Meyer, *ibid.*, **37**, 2553 (1904).
[252] v. Pechmann and Nold, *ibid.*, **29**, 2588 (1896).
[253] Conant and Cook, *J. Am. Chem. Soc.*, **42**, 830 (1920).
[254] Hofmann, *Ann.*, **250**, 316 (1888).
[255] Borsche and Rantsheff, *ibid.*, **379**, 152 (1911).
[256] Fries and Empson, *ibid.*, **389**, 350 (1912).
[257] Englert and McElvain, *J. Am. Chem. Soc.*, **56**, 700 (1934).

N_3S.[258] (*d*) Acetallylthiocarbimide, $C_7H_{13}O_2NS$ (from the reaction of sodium hydroxide with carbon bisulfide and aminoacetal), is heated for 1 hr. with 8-aminoquinoline, and the product therefrom is heated with 5 *N* sulfuric acid.[259] (*e*) Indene-1-carboxylic acid chloride with diazomethane gives $C_{12}H_{10}N_4O$.[260] (*f*) Allyl thiocyanate is treated with hydrazine hydrate in alcohol in an ice bath, the product treated with benzoylchloride, and the mono-benzoylated product then treated with acetyl chloride on a water bath. The composition of the final product is $C_{11}H_{11}N_3S$.[261] (*g*) *o*-Phenylenediamine is treated with acetic anhydride, the diacyl derivative is allowed to react with nitric acid, the product is then boiled with 4 *N* hydrochloric acid, and this material, in turn, is treated with iron powder and hydrochloric acid. The compound finally obtained is $C_8H_9N_3$.[262] (*h*) Ethyl benzoylacetate is treated with sodium nitrite in acetic acid, the product is allowed to react with zinc and aqueous sulfuric acid, and the second product is treated with nitrous acid. The last compound, $C_{11}H_{10}N_2O_3$, yields $C_{12}H_{13}N_5O_3$ when allowed to react with semi-carbazide.[263] (*i*) Compounds that have the formula $C_9H_7NO_2$ and $C_{11}H_7N_3O_2$ are obtained when diazomethane reacts with isatin[264] and with 1,2-naphthoquinone,[265] respectively. (*j*) The product of reaction of benzil and diazomethane has the composition $C_{15}H_{12}O_2$. (This reaction is not shared by diacetyl or by acetonylacetone.)[266] (*k*) Ethanol, formaldehyde, and dry hydrochloric acid give a product of the composition C_3H_7OCl, which, by reaction with cuprous cyanide and then with phenylmagnesium halide, gives a compound of the composition $C_{10}H_{12}O_2$. This compound in turn reacts with anhydrous hydrogen cyanide and ammonia. The product, $C_{11}H_{14}N_2O$, is converted to $C_{12}H_{15}N_3O_2$ by solution in glacial acetic acid and treatment with an equivalent amount of potassium cyanate at 65 to 70°. Treatment with 20 per cent hydrochloric acid gives a final product, $C_{12}H_{14}N_2O_3$.[267] (*l*) Benzoylhydrazine is heated at 180° for 3 hr. with phenylacetic acid in the presence of a few drops of pyridine, and the product of this reaction is heated with aniline at 180 to 190° for 3 hr. in the presence of fused zinc chloride. The composition of the final product is $C_{21}H_{17}N_3$.[268] (*m*) Dibenzylidene hydrazine, $C_6H_5CH{=}N{-}N{=}CHC_6H_5$, is heated at 127° with three molecular quantities of acetic anhydride for 35 hr. The reaction mixture is then allowed to stand for 2 weeks, during which time the crystals that first formed redissolve. Distillation of the final product yields a fraction that boils at 165 to 169° (624 mm.) and has the empirical composition $C_4H_6N_2O$.[269] (*n*) ω-Aminoacetophenone hydrochloride is dissolved in water and treated with benzoyl chloride and aqueous potassium hydroxide, and the product of that reaction is treated with concentrated sulfuric acid on the water bath for 2 min. and then poured into water.[270]

---

[258] Hofmann, *Ber.*, **20**, 2251 (1887).

[259] Easson and Pyman, *J. Chem. Soc.*, 1806 (1932).

[260] Knowles, Buck, and Elderfield, *J. Org. Chem.*, **7**, 374 (1942).

[261] Pulvermacher, *Ber.*, **27**, 613 (1894).

[262] Phillips, *J. Chem. Soc.*, 172 (1928).

[263] Wolff and Hall, *Ber.*, **36**, 3612 (1903).

[264] Heller, *ibid.*, **52**, 741 (1919); **59**, 704 (1926); Arndt, Eistert, and Ender, *ibid.*, **62**, 44 (1929).

[265] Fieser and Hartwell, *J. Am. Chem. Soc.*, **57**, 1479 (1935).

[266] Biltz and Paetzold, *Ann.*, **433**, 81 (1923); **436**, 154 (1924); Arndt, Amende, and Ender, *Monatsh.*, **59**, 202 (1932).

[267] Rigler and Henze, *J. Am. Chem. Soc.*, **58**, 474 (1936).

[268] Bhagat and Ray, *J. Chem. Soc.*, 2357 (1930).

[269] Ekeley and Lefforge, *J. Am. Chem. Soc.*, **58**, 562 (1936).

[270] Robinson, *J. Chem. Soc.*, **95**, 2167 (1909).

(*o*) Ethyl formate is allowed to stand overnight with aminoacetal, the mixture heated for 1 hr. at 100°, and the product then heated with phosphorus pentasulfide for 10 min. in an oil bath at 160°.[271]

5. 2-Amino-4-nitrotoluene is the starting material for the following sequence of reactions: diazotization, reflux, reduction with stannous chloride (*A*), diazotization, hydrolysis in concentrated sulfuric acid which contains boric acid, coupling with phenyldiazonium chloride, reduction with sodium hydrosulfite, aerial oxidation (*B*), and addition of sodium bisulfite (*C*).

What are the products at *A*, *B*, and *C*, if the empirical formulas of these products are $C_7H_7N_3$, $C_7H_4N_2O_2$, and $C_7H_6N_2SO_5$, respectively?[272]

6. (*a*) Benziminoethyl ether, $C_6H_5C(=NH)OC_2H_5$ (how prepared?), is allowed to stand with β-bromoethylamine hydrobromide (how prepared?) for many days in the presence of sodium methoxide. The mixture is then treated with alcoholic hydrobromic acid, and the salt of a base that has the composition $C_9H_{10}N_2$ is isolated. What is the probable structure? (*b*) 2-Ethoxy-Δ^1-homopiperidine, $\overline{(CH_2)_5\text{—}N{=}C}\text{—}OC_2H_5$ (how prepared?), is treated with β-bromoethylamine as in the above example. What is the structure of the product, $C_8H_{14}N_2$?[273]

7. The compound (2-thio-3-methyl-4-ketotetrahydro-5-thiazolyl)(2′-thio-3′-methyl-4′-ketotetrahydro-5′-thiazolylidine)-*meso*methylmethane is claimed to be a dye intermediate that is useful in photography. What is the formula of this compound and how is it probably prepared? Do the same for 3-ethyl-5-[2-(3-methyl-2(3)-benzothiazolylidene) ethylidene]rhodanine.[274]

8. Each of the empirical formulas listed below represents a compound with one heterocyclic ring. Suggest a structural formula for an azole that would be consistent with the composition indicated and that could be prepared from readily available reagents.

$C_{11}H_{13}ON$[226a]

$C_{11}H_7ON$[275]

$C_{10}H_9ON$[276]

$C_{12}H_{12}O_2N_2$[277]

$C_{19}H_{13}N_3O_2$[278]

$C_{21}H_{14}N_2$[279]

9. What is the product of the reactions of the following compounds of the azole type? (*a*) 2-Aminothiazole-4,5-dicarboxylic acid heated at 170 to 200° with resorcinol.[280] (*b*) 3-Methyl-1-phenyl-4-pyrazolone with isatin-α-anilide.[281] (*c*) 1-Methyl-5-chloroimidazole heated for 8 hr. at 135 to 140° with formalin.[282]

---

[271] Gabriel and Bachstez, *Ber.*, **47,** 3169 (1914).

[272] Fieser, *J. Am. Chem. Soc.*, **48,** 1097 (1926); Fieser and Ames, *ibid.*, **49,** 2604 (1927).

[273] Stollé, Merkle, and Hanusch, *J. prakt. Chem.*, **140,** 59 (1934).

[274] Kendall and Fry, British patent 540,577, Oct. 22 (1941); *C.A.*, **36,** 4041 (1942); British patent 519,895, Apr. 9 (1940); *C.A.*, **36,** 715 (1942).

[275] Fischer, *J. prakt. Chem.* [2], **73,** 419 (9906).

[276] Gabrield, *Ber.*, **43,** 1280 (1910).

[277] Knoor, *ibid.*, **20,** 1906 (1887).

[278] Fries, *Ann.* **454,** 303 (1927).

[279] Cook and Jones, *J. Chem. Soc.*, 278 (1941).

[280] De, *J. Indian Chem. Soc.*, **7,** 617 (1930).

[281] Felix and Friedländer, *Monatsh.*, **31,** 55 (1910).

[282] Grindley and Pyman, *J. Chem. Soc.*, 3128 (1927).

10. Devise methods for preparing the following open-chain compounds by processes that employ an intermediate azole compound. (*a*) Furanacetic acid.[283] (*b*) Propylenediamine-1,2, $C_3H_8N_2$, from dextrose.[284] (*c*) 1,2,4-Triaminobutane trihydrochloride.[285] (*d*) Furylalanine, $C_4H_3O\,CH_2CH(NH_2)COOH$.[286]

11. (*a*) α-Chloroquinoline is heated with pure hydrazine hydrate at 140°, and the product is then treated with phenylisothiocyanate in alcohol. The crystals which thus form have the composition $C_{16}H_{14}N_4S$ and change at 150° to a weakly acidic compound that dissolves easily in alkali but not in ammonia and has the composition $C_{10}H_7N_3S$. Warm dilute nitric acid converts this last product to a compound identical with that obtained when α-quinolylhydrazine is boiled for an hour with anhydrous formic acid. What compounds are involved in these changes?[287] What is the product of the action of the hydrazine compound with nitrous acid? (*b*) A concentrated acetic acid solution of benzoylacetone, $C_6H_5C(O)CH_2C(O)CH_3$, is treated with a concentrated solution of sodium nitrite. The product is then reduced with zinc and sulfuric acid. Yellow-green crystals are obtained which melt at 65 to 66° and have the composition $C_{10}H_8N_2O_2$. When the product is treated with ammonium hydrosulfide and the solution is saturated with hydrogen sulfide, two isomeric compounds result. They have the composition $C_{10}H_8N_2OS$ and form isomeric semicarbazones. What conclusions as to structures might be drawn from these facts? (*c*) 1,2,4-Triazole undergoes ring scission in the presence of benzoyl chloride and sodium carbonate. Picture the probable intermediate steps in the process.[289]

12. Suggest methods for preparing the following: (*a*) Two isomeric N-phenyltriazoles.[290] (*b*) Two isomeric angular 2-aminonaphthathiazoles.[80] (*c*) Two isomeric methylphenyloxazoles or thiazoles.[3]

13. Vitimidazole, 4-methyl-5(β-hydroxyethyl)imidazole, is the imidazole analogue of the thiazole part of thiamine, but lacks the characteristic activity of the thiazole compound. Devise a method for preparing $CH_3C(O)CH_2CH_2CH_2OH$ and show steps for converting this intermediate to the imidazole compound.[291]

14. Imidazolylacetic acid, $\overline{C_3H_3N_2}CH_2COOH$, is the imidazole analogue of indoleacetic acid. It has been suspected of being a possible metabolic intermediate. Suggest a method for its synthesis.[292]

15. The product of the reaction of lin.-naphthotriazole with chloroacetyl chloride in boiling benzene has the composition $C_{12}H_8OClN_3$. Treatment of this product with aluminum chloride in nitrobenzene liberates a gas and forms $C_{12}H_9O_2N$. Suggest structures for those substances and a method for synthesis of the last compound from chloroacetic acid which would confirm the conclusion as to structure.[293]

16. Isatin is heated with rhodamine in a glacial acetic acid, acetic anhydride, sodium acetate mixture. The product (*A*) so prepared is then heated with one equivalent of alcoholic potassium hydroxide for 1 hr. A red solid, which is a mono potassium salt, $C_{11}H_5KN_2O_2S_2$, (*B*) is obtained. When this salt is suspended in water, hydrolysis occurs and product *A* is obtained. If three instead of one equivalent of alcoholic potassium hydroxide are used, a canary-yellow crystalline solid is obtained as a dipotassium salt, $C_{10}H_5K_2NO_3S$, (*S*). Acidification yields the product (m.p. 166° corr.) that has the composition, $C_{10}H_7NO_3S$, (*D*). What is the probable constitution of the four compounds indicated? The products of the action of *D* with aniline, hydroxylamine, and phenylhydrazine are $C_{16}H_{12}N_2O_3$, $C_{10}H_6N_2O_3$, and $C_{16}H_{11}N_3O_2$, respectively.[294]

---

[283] Plucher and Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).

[284] Windaus and Knoop, *Ber.*, **38**, 1166 (1905).

[285] Windaus, Dorries, and Jensen, *ibid.*, **54**, 2745 (1921).

[286] Granacher, *Helv. Chim. Acta*, **5**, 610 (1922).

[287] Marckwald and Meyer, *Ber.*, **33**, 1885 (1900).

[288] Wolff, Bock, Lorentz, and Trappe, *Ann.*, **325**, 129 (1902); Wolff, *ibid.*, **394**, 23 (1912); Staudinger, *Helv. Chim. Acta*, **4**, 239 (1920).

[289] Heller, *Ber.*, **40**, 114 (1907).

[290] Dimroth, *ibid.*, **35**, 1035, 1045 (1902); v. Pechmann, *Ann.*, **262**, 290 (1891).

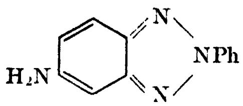
[291] Fox, Sargent, and Buchman, *J. Am. Chem. Soc.*, **67**, 496 (1945).

[292] Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

[293] Fries, Walter, and Schilling, *Ann.*, **516**, 248 (1935).

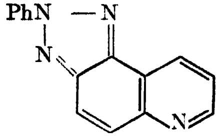
17. Devise methods for synthesizing from a readily available material the compound illustrated as *A* below, and from that compound *B* and *C* in sequence. Give appropriate names to the compounds.[295a]

A

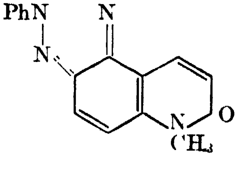


Ph = C_6H_5.

B



C



18. What is the probable product that results from mononitration of the acetyl derivative of *A* in the problem above? In the preparations listed below, give the structure and name of the compound produced. When *A* is diazotized and the diazonium sulfate solution heated to boiling in aqueous sulfuric acid, a small amount of the hydroxy product is obtained, but the larger quantity is a red compound, insoluble in alkali, which has the empirical formula $C_{24}H_{16}N_8O$. When *A* is heated in alcohol with an equal part of benzaldehyde, a precipitate, the composition of which is $C_{19}H_{14}N_4$, is obtained; and this precipitate, when boiled in acetic acid, gives a yellow product (m.p. 315°), which has the composition $C_{31}H_{21}N_7$. Bromine converts this product to $C_{31}H_{19}N_7$. When the above mentioned hydroxy compound, derived from *A*, is (*a*) treated with oxalyl chloride and aluminum chloride in carbon bisulfide, a greenish-yellow product (m.p. 203°) with the composition $C_{14}H_7N_3O_3$ is obtained. When the hydroxy compound is (*b*) treated with benzaldehyde in alcoholic solution and saturated with dry hydrochloric acid, a compound with the composition $C_{31}H_{22}O_2N_6$ is obtained which changes to one with the composition $C_{31}H_{20}ON_6$ when heated in toluene with phosphorus oxychloride.[295a]

19. A chloroform solution of *p*-aminobenzonitrile is stirred with an aqueous suspension of thiocarbonyl chloride and the product then isolated and treated with alcoholic ammonia. This compound, in turn, is dissolved in chloroform and treated with bromine. Analysis of the reddish-brown crystalline mass shows 64.6 per cent of bromine. This compound is suspended in sulphurous acid and treated with sulfur dioxide, after which a white flaky precipitate (analysis S = 18.3 per cent) is obtained from the colorless solution by addition of ammonia. What is the probable structure of the compounds obtained in this sequence of reactions.[295b]

---

[294] Gränacher and Kouniniotis, *Helv. Chim. Acta.*, **11**, 1241 (1928); Jones and Henzl, *J. Am. Chem. Soc.*, **64**, 1669 (1942).

[295] (*a*) Fries, Sudhoff, and Brettschneider, *Ann.*, **454**, 131 (1927); (*b*) Dyson, Hunter, and Morris, *J. Chem. Soc.*, 1186 (1927).

20. Suggest a method that will show the equivalence of the 3- and 5-positions in N-unsubstituted pyrazoles.[296]

21. Suggest a synthesis which will show that bromination of thiazole at high temperatures introduces a bromine atom in the 2-position.[297]

22. Monochloroacetone in the presence of excess ammonium thiocyanate yields a product that has the empirical formula $C_4H_6N_2S$. What tests might be applied to distinguish between 2-amino-4-methylthiazole and thiocyanopropimine, $HN{=}C(CH_3)CH_2SCN$, as a possible formula?[298]

23. Citraconic acid, $HOOCC(CH_3){=}CHCOOH$ (how obtained?), reacts with diazomethane to give a pyrazoline compound. Suggest two possible structures and a simple method for distinguishing between them. (Note: The product actually obtained is the one that results from the union of the carbon atom of diazomethane to the carbon atom next to primary carboxylic acid.)[299]

24. What is the probable structure of the product of the reaction of butadiene with diazomethane?[300]

25. What are the compounds formed from the reaction of potassium thiocyanate with α-aminopropiophenone (how prepared?) and α-phenyl-α-aminoacetone (how prepared?), respectively? What bearing might these two syntheses have on the question of the structure of imidazoles?[301]

26. Formaldehyde reacts with 4(5)-methylimidazole in a sealed tube at 120° to form 4(5)-methyl-5(4)-hydroxymethylimidazole. How would you show that the product is not a β-ethanol derivative?[302]

27. Methyl ethyl ketone with ethyl oxalate forms a substituted pyruvic ester. Show how to determine whether this condensation has taken place on the methyl or ethyl group of the ketone by use of an appropriate heterocyclic compound derived from the ester.[303]

28. Bromination of 4-methylimidazole may introduce a halogen atom in the 2- or 4-position. Suggest a synthesis that will give a proof of the position taken.[304]

29. From each of the following cases draw an opinion as to a probable structure of the compound from the decomposition products indicated. Suggest a method for obtaining the compound. (*a*) $C_3H_4O_3N_2$ in the presence of alkali decomposes to acetylene, nitrogen, carbon dioxide, and water.[305] (*b*) $C_2H_4N_4$ in the presence of benzoyl chloride and alkali decomposes to 2 molecules of $C_{14}H_{12}N_2O_2$ and 2 molecules of CH_2O_2.[306] (*c*) CH_3N_5 decomposes to hydrazine, ammonia, nitrogen, and carbon dioxide when heated with concentrated hydrochloric acid at 200°.[307] (*d*) $C_3H_6N_4$ decomposes to hydrazine, ammonia, acetic acid, and carbon dioxide when heated with dilute sulfuric acid at 180°.[306,308]

---

[296] Knorr, *Ann.*, **279**, 188 (1894).

[297] Wibaut and Jansen, *Rec. trav. chem.*, **53**, 77 (1934).

[298] Hantzsch and Weber, *Ber.*, **20**, 3118, 3336 (1887).

[299] v. Pechmann and Burkard, *ibid.*, **33**, 3597 (1900).

[300] Muller and Roser, *J. prakt. Chem.*, **133**, 291 (1931).

[301] Gabriel, *Ber.*, **41**, 1926 (1908).

[302] Windaus, *ibid.*, **42**, 758 (1909); Ewins, *J. Chem. Soc.*, **99**, 2052 (1911).

[303] Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941).

[304] Pyman and Timmis, *J. Chem. Soc.*, **115**, 494 (1923).

[305] Jones and Kenner, *ibid.*, 363 (1933).

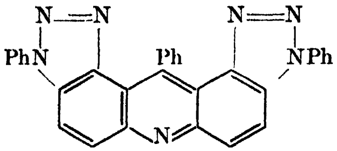
[306] Thiele and Heidenreich, *Ber.*, **26**, 2598 (1893); Thiele and Manchot, *Ann.*, **303**, 39 (1898).

[307] Thiele and Ingle, *ibid.*, **287**, 235, 245 (1893).

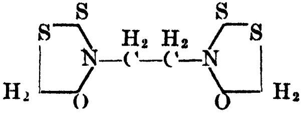
[308] Thiele and Heidenreich, *Ber.*, **26**, 2598 (1893).

30. Suggest a method for the synthesis of the following compounds: *A*,[309] *B*,[310] *C*,[311] *D*,[312] *E*,[313] *F*[314] from readily available materials. Give appropriate names for the compounds.

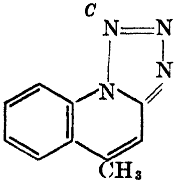
A



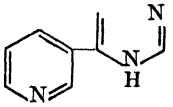
B



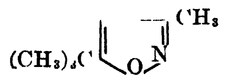
C



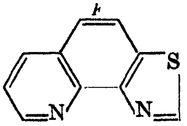
D



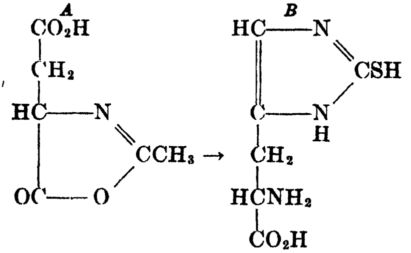
E



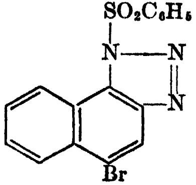
F



31. Suggest a method for obtaining *A* below and a sequence of reactions for converting *A* to *B*.[315] Name the compounds.



32. 1-Benzenesulfonyl-4-bromo-naphtho[1,2]triazole (how prepared?) melts at 156°. When treated with benzenesulfonyl chloride and triethylamine in boiling benzene, this compound (shown at the right) rearranges to an isomeric compound that melts at 209° and is less reactive.



What is a possible structure of the higher melting product?[316]

---

[309] Fries, Sudhoff, and Bretschneider, *Ann.*, **454**, 131 (1937).

[310] Naegele, *Monatsh.*, **33**, 941 (1912).

[311] Marckwald and Chain, *Ber.*, **33**, 1895 (1900).

[312] Ochiai and Ikuma, *ibid.*, **69**, 1147 (1936).

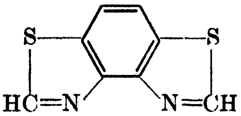
[313] Couturier, *Compt. rend.*, **150**, 928 (1910).

[314] Erlenmeyer and Ueberwasser, *Helv. Chim. Acta*, **23**, 328 (1940).

[315] Harrington and Overhoff, *Biochem. J.*, **27**, 338 (1933).

[316] Morgan and Godden, *J. Chem. Soc.*, **97**, 1702 (1910).

33. Suggest a method for the synthesis of the compound pictured below. Under what name would the compound be listed in *Chemical Abstracts*? Where would it be found in Beilstein? With what other heterocyclic compound could its properties be compared?[317]



34. N-Nitrosoaromatic amines undergo a rearrangement to *p*-nitrosoanilines when treated with alcoholic hydrochloric acid. When β-naphthylethylnitroso amine is thus treated, the product obtained is $C_{10}H_{12}N_2 \cdot HCl$.[318] What changes are involved? What would have been the character of the product had an α-naphthylamine been used?

---

[317] Erlenmeyer and Ueberwasser, *Helv. Chim. Acta*, **23**, 328 (1940).

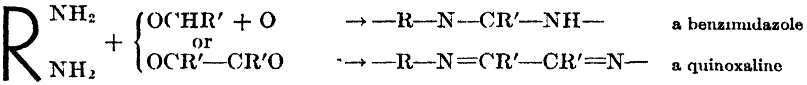
[318] Fischer and Hepp, *Ber.*, **20**, 1247 (1887).

CHAPTER XV

THE AZINES AND RELATED COMPOUNDS

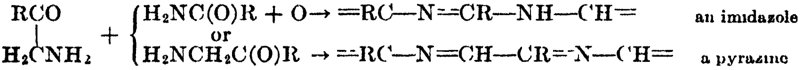
Six-membered rings with two or more hetero atoms, one of which is nitrogen, are known as azines.[1] The number of possible combinations is extremely large. The members with two nitrogen atoms are widely distributed in nature. Some of the synthetic products that contain an oxygen or nitrogen atom are commercially important.

The methods for preparation often bear a striking resemblance to those used for the azoles, except for provision for an additional atom in the ring. Usually this extra atom is in the form of a methylene or carbonyl group, or in the form of a carboxyl group in place of an amino or chloro group. A few illustrations will suffice. The condensation of an aldehyde with *o*-phenylenediamine to form a benzimidazole is paralleled by the condensation of a dialdehyde or diketone to form a quinoxaline. Similarly, the formation of an imidazole by the reaction of an α-aminoketone or aldehyde is the same type of reaction as the formation of a pyrazine, save for the extra methylene group in one of the reagents; the preparation of a thiazole from an α-chloroketone or aldehyde and a thioacetamide is much the same as the preparation of a thiazine from a keto ester and the thioamide, save

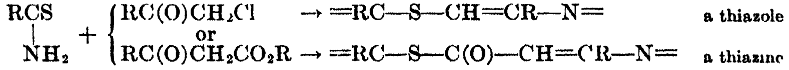


$$R\begin{matrix}NH_2\\ \\NH_2\end{matrix} + \begin{cases} OCHR' + O & \rightarrow -R-N-CR'-NH- \quad \text{a benzimidazole}\\ \quad\text{or} & \\ OCR'-CR'O & \rightarrow -R-N=CR'-CR'=N- \quad \text{a quinoxaline}\end{cases}$$

Large and small R = a benz radical, R′ = H, alkyl or aryl. The products in the above two reactions as well as in the ones below, are represented by a chain of atoms, the extreme ends of which are considered to be joined in a ring system.



$$\begin{array}{l}RCO\\ \;|\\ H_2CNH_2\end{array} + \begin{cases} H_2NC(O)R + O \rightarrow =RC-N=CR-NH-CH= & \text{an imidazole}\\ \quad\text{or} & \\ H_2NCH_2C(O)R \rightarrow =RC-N=CH-CR=N-CH= & \text{a pyrazine}\end{cases}$$

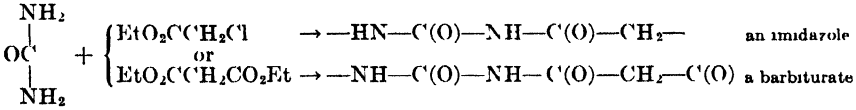


$$\begin{array}{l}RCS\\ \;|\\ NH_2\end{array} + \begin{cases} RC(O)CH_2Cl \rightarrow =RC-S-CH=CR-N= & \text{a thiazole}\\ \quad\text{or} & \\ RC(O)CH_2CO_2R \rightarrow =RC-S-C(O)-CH=CR-N= & \text{a thiazine}\end{cases}$$

---

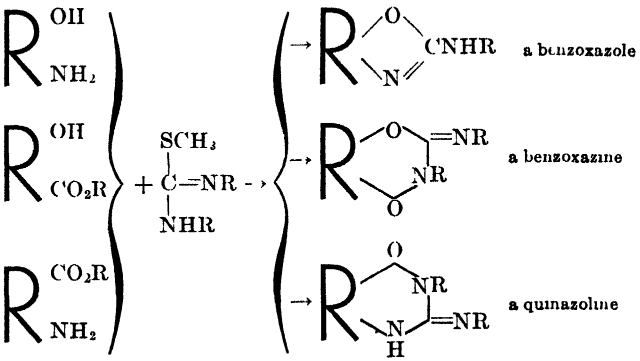
[1] The endings for the lowest state of hydrogenation for ring systems with 3,4,5,6, 7,8,9 atoms irrespective of whether or not hetero atoms are present are *-ete*, *-ole*, *-ine*, *-epine*, *-ocine*, *-onine*, and *-ecine*, respectively; those for the highest state of hydrogenation are *-etidine* and *-olidine* for the first two, respectively; and the larger rings are designated as *di-*, *tetra-*, *hexa-*, etc., depending on the number of atoms of hydrogen present. Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, 1940.

for the carboalkoxy group in place of a chloro atom; and the synthesis of an azolone by the reaction of an α-chloro ester with urea is the same class of reaction as the well-known synthesis of barbituric acids, except for the use of a carbethoxy group in place of a chloro atom. This effect



$$\begin{matrix}NH_2\\ |\\ OC\\ |\\ NH_2\end{matrix} + \begin{cases} EtO_2CCH_2Cl \rightarrow -HN-C(O)-NH-C(O)-CH_2- & \text{an imidazole}\\ \text{or} & \\ EtO_2CCH_2CO_2Et \rightarrow -NH-C(O)-NH-C(O)-CH_2-C(O) & \text{a barbiturate}\end{cases}$$

of the replacement of a hydroxyl or amino group by a carbethoxy is well shown by the reactions below in which the carbethoxy group is used in place of the amino group in o-aminophenol as in salicylic acid, or is used in place of the hydroxyl group, as in anthranilic acid, to give a benzoxazine or a quinazoline respectively.



Wherever a carboalkoxy group has been used, the ring contains a keto group. This substituent is converted readily to a chloro group by means of phosphorus oxychloride. The halogen is then eliminated by reduction with zinc and hot water or with hydriodic acid and phosphorus.

The reactions that the azines undergo are, in general, predictable from the behavior of other heterocyclic compounds that have similar functional groups inside or outside the ring.

OXAZINES AND THIOXINES

Morpholine is tetrahydro-1,4-oxazine. Its common name was given by its discoverer, Knorr,[2] who was then engaged in studies of morphine and believed that the reaction of diethanolamine with hydrochloric acid at 160° had produced the mother substance of the alkaloid molecule. The compound may also be obtained from the action of sulfuric acid on triethanolamine, itself derived from ammonia and ethylene oxide.

---

[2] Knorr, *Ber.*, **22**, 2081 (1889); *Ann.*, **301**, 1 (1898).

Morpholine[3] boils at 128.3° and has a specific gravity of 1.0016. It is soluble in water in all proportions but not in strong caustic solution. It is noted for its solvent powers, which are better even than those of dioxane. It dissolves dyes and other molecules of comparatively large molecular weight, in addition to a wide variety of organic compounds.

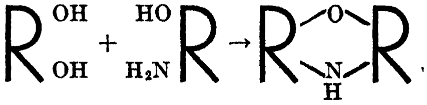
The compound behaves as a secondary amine.[3] It forms a nitroso derivative, a benzoyl derivative from benzoyl chloride and sodium hydroxide, a urea from potassium cyanate and the chlorhydrate, the methiodide of methylmorpholine by the reaction with methyl iodide, a β-ethanolamine with ethylene oxide, amides[4] with formic or acetic acids, and a formic ester with methyl chloroformate.[4]

Morpholine serves as a condensing agent comparable to piperidine and secondary amines. It causes the Mannich reaction[5] between formaldehyde and compounds with active hydrogen such as those in ketomethylene groups. Acetone, paraformaldehyde, and morpholine hydrochloride in alcohol, for example, give the hydrochloride of 1-morpholinobutan-3-one. Phenol, formaldehyde, and morpholine give the 2,4,6-trisubstituted product,[6] $[O(CH_2CH_2)_2NCH_2]_3C_6H_2OH$, comparable to the one obtained when dimethylamine is used as the condensing agent.

As a derivative of β-ethanolamine, it has some physiological action. There is a slight antipneumococcic activity. Esters of morpholine alcohols such as from 2-alkoxycinchoninic acid have some anesthetic properties.[7]

Morpholine forms ammonium soaps with oleic and stearic acids, which are particularly useful for stable oil in water emulsions.[3] When spread in films, the morpholine gradually volatilizes so that the film cannot be reemulsified.

Phenoxazines.—*o*-Aminophenol condenses with pyrocatechol[8] at 260° or with the hydrochloride of *o*-aminophenol[9] to give phenoxazin. Compounds of this type can be prepared by a stepwise process[10] as shown below:



---

[3] Wilson, *Ind. Eng. Chem.*, **27**, 867 (1935).

[4] Medard, *Bull. soc. chim.* [5], **3**, 1343 (1936).

[5] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939); *C.A.*, **33**, 5855 (1939).

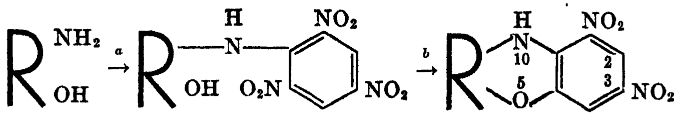
[6] Bruson and MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).

[7] Gardner and Hammel, *ibid.*, **58**, 1360 (1936).

[8] Bernthsen, *Ber.*, **20**, 942 (1887).

[9] Kehrmann and Neil, *ibid.*, **47**, 3107 (1914).

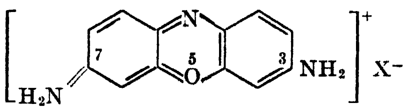
[10] Turpin, *J. Chem. Soc.*, **59**, 721 (1891); Misslin and Bau, *Helv. Chim. Acta*, **2**, 295 (1919).



[a] Picryl chloride. [b] Hot alkali causes loss of HNO_3.

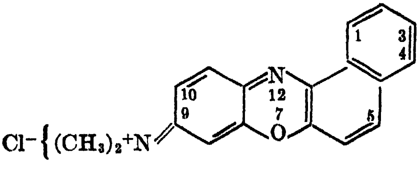
o-Aminophenol and 2,4,6-trinitroanisole and alcoholic alkali at 70° also give 1,3-dinitrophenoxazine.

Phenoxazine melts at 156° and forms an acetyl derivative. Nitration of acetylphenoxazine gives the 3,7-dinitro product,[11] which by reduction with stannous chloride–hydrochloric acid gives a leuco product, oxidizable by air to a dye. Oxidation of hydroxy-*p*-phenylenediamine gives the same product, but in poor yield. The dye is violet colored in dilute acid solution and a strong fluorescent red in concentrated acid.



This dye is not stable. It is related, however, to a large number of dyes,[12] some of which are particularly valuable or useful in other ways. Figure 1 shows a cation or anion of a number of related compounds, together with the corresponding indamine compound, which can be regarded as the parent type. One resonance form only of the dye is illustrated. In the case of the heterocyclic compounds, one of the resonance forms may have an orthoquinoid structure also. Acridine dyes have a similar constitution except for a carbon atom in place of oxygen or sulfur in the bridge between the two rings.

Meldola's blue[13] is prepared by condensation of *p*-nitrosodimethylaniline with β-naphthol, followed by oxidation. The product was once used to make a dye for tannined cotton and leather. The dust is very irritating to the mucous membrane. The compound has a very reactive hydrogen atom in the 5-position. It condenses with bases such as *p*-aminodimethylaniline or dimethylamine to form the new blue or new



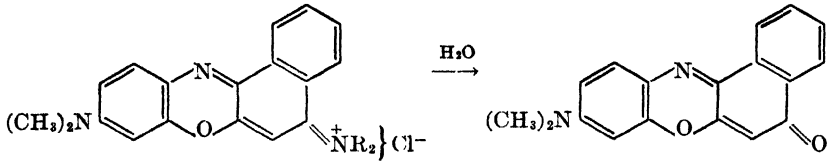
---

[11] Kehrmann and Saager, *Ber.*, **36**, 475 (1903); Kehrmann and Sandoz, *ibid.*, **50**, 1680 (1917).

[12] Cain and Thorpe, "Synthetic Dyestuffs," Charles Griffin & Company, Ltd., London, 1933.

[13] Meldola, *Ber.*, **12**, 2065 (1879).

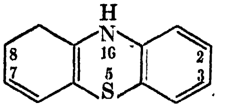
methylene blue GG, respectively. Long boiling with mineral acid in the presence of air also converts Meldola's blue to phenonaphthoxazone.[14] The same compound is obtained from new blue or new methylene blue GG by hydrolysis.



Because of this conversion to an oxazone, dyes of the phenonaphthoxazine type are capable of a differential staining[14]; on fat they are red, and on protein, they are blue. The phenoxazine dyes do not have such a property.

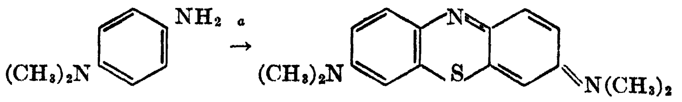
The gallocyanines are prepared by condensing *p*-nitrosodimethylaniline hydrochloride with gallic acid in boiling methanol. They are used considerably in printing.

Phenothiazine is prepared by fusion of diphenylamine with sulfur. The pure material melts at 185.11°.[15] It is a remarkable anthelmintic, is



very valuable as an insecticide, and is useful in therapeutics. It is more toxic than rotenone to mosquito larvae and is fully as effective as lead arsenate on codling-moth larvae.[16]

Methylene blue is widely used as a stain in biological work and has some value as an antiseptic and dye. It is prepared by the action of an oxidizing agent on *p*-dimethylaminoaniline, dimethylaniline, and thiosulfuric acid. The reaction proceeds through an intermediate sulfur compound as well as through other obvious stages.[17]



The starting compound is prepared by reduction of *p*-nitrosodimethylaniline.

[a] Treatment with ferric chloride in the presence of H_2S. A better method is treat with thiosulfuric acid, isolate the intermediate thiosulfuric acid, $(CH_3)_2NC_6H_3(NH_2)S_2O_3H$, oxidize a mixture of this acid and dimethylaniline, and heat the indamine product in boiling dilute sulfuric acid.

---

[14] Thorpe, *J. Chem. Soc.*, **91**, 324 (1907).

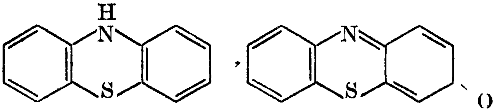
[15] Smith and Nelson, *J. Am. Chem. Soc.*, **64**, 461 (1942).

[16] Beeler, *Bull. Nat. Formulary Comm.*, **10**, 84 (1942); Roark, *Chem. Eng. News*, **22**, 1464 (1944); Smith, *Ind. Eng. Chem.*, **34**, 499 (1942).

[17] Bernthsen, *Ann.*, **230**, 73 (1885).

Treatment of the dye with potassium dichromate at 70° gives a dimethylene blue chromate. Oxidation of this compound with bichromate and boiling hydrochloric acid without access of air eliminates one methyl group as formaldehyde to give a trimethyl product known as methylene azure B. Further oxidation in acid solution removes a second methyl group on the same nitrogen.

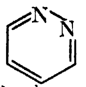
Hydroxyphenylthiazone, known also as thional,[18a] is made by treatment of phenothiazine with hydrogen peroxide in aqueous alcoholic hydrochloric acid.



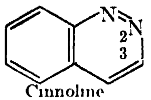
The compound is valuable as an oxidation-reduction indicator.

PYRIDAZINES

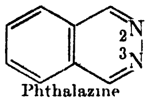
Six-membered monocyclic systems with two adjacent nitrogen atoms are known as pyridazines. The condensed bicyclic systems are known as cinnoline and phthalazine, depending on the positions of the nitrogen atoms



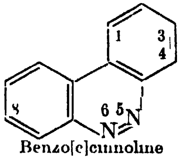
Pyridazine



Cinnoline

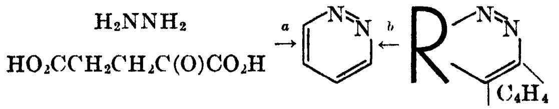


Phthalazine



Benzo[c]cinnoline

The simplest member of this series is prepared by standard processes from α-ketoglutaric acid[18b] or from benzocinnoline[19] by oxidation and decarboxylation.



[a] Condensation, oxidation by Br₂, decarboxylation, treatment with $POCl_3$ and then with HI.

[b] $KMnO_4$, 15 per cent HCl at 100° to remove two carboxyl group, 5 per cent HCl at 200° to complete decarboxylation.

Pyridazine melts at −8° and boils at 208°.

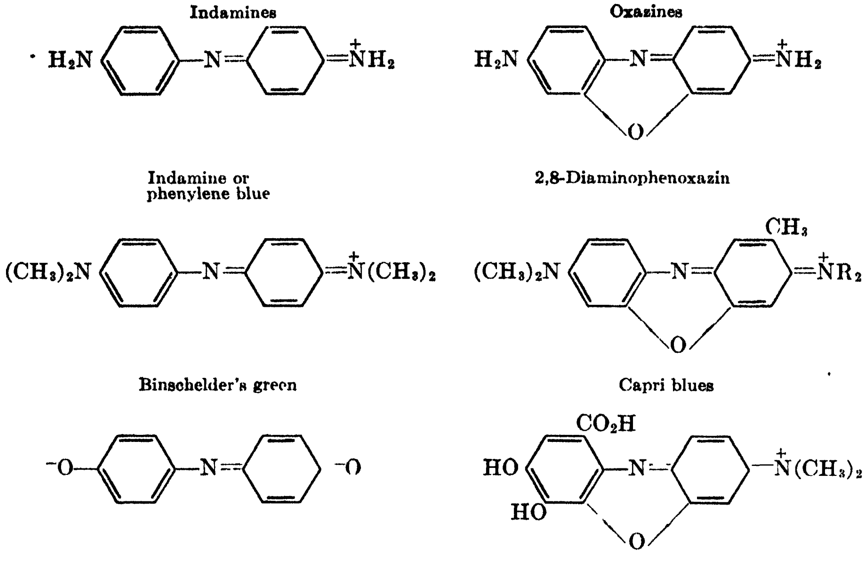
Cinnolines can be prepared[20] by the Widman-Stoerner reaction in which an *o*-aminoarylethylene is diazotized. Cyclization usually occurs spontaneously. *o*-Aminocinnamic acid gives no cinnoline, however.

[18a] De Eds and Eddy, *J. Am. Chem. Soc.*, **60**, 1446 (1938).

[18b] Paal and Schulze, *Ber.*, **33**, 3785, 3796 (1900).

[19] Tauber, *ibid.*, **28**, 451 (1895); Stoermer and Fincke, *ibid.*, **42**, 3115 (1909); Stoermer and Gaus, *ibid.*, **45**, 3112 (1912).

[20] Widman, *ibid.*, **17**, 722 (1884); Stoermer and Gaus, *ibid.*, **43**, 3104 (1912); Simpon, *J. Chem. Soc.*, 447 (1943).



Indamine or phenylene blue

2,8-Diaminophenoxazin

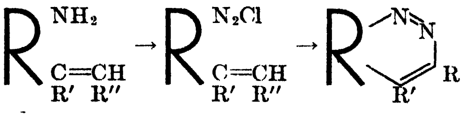
Bindschedler's green

Capri blues

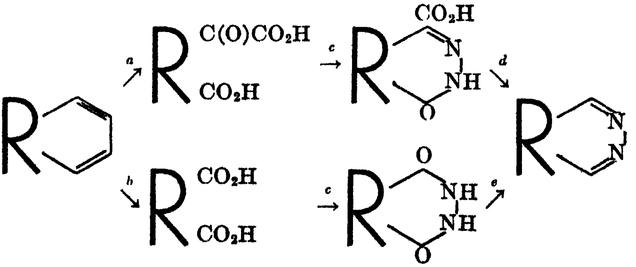
Indophenol

Gallocyanines

FIG. 1.—Comparison of structure of some azine

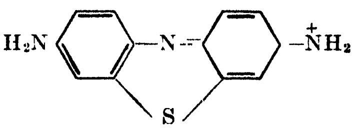


Phthalic acids or appropriately *o*-substituted benzoic acids condense with hydrazine to give pyridazones, known as *phthalhydrazides* if two keto groups are present. The formation of mono and diketo products is illustrated below by the reaction of hydrazine with phthalonic acid and



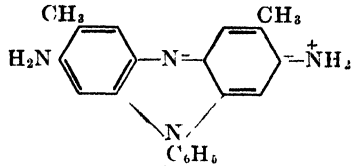
[a] $Ca(MnO_4)_2$. [b] $KMnO_4$. [c] N_2H_4. [d] Decarboxylation, $POCl_3$, HI + P. [e] $POCl_3$, HI + P.

Thiazines

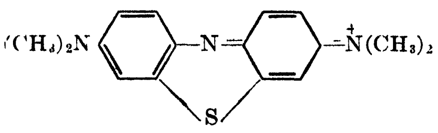


Lauth's violet

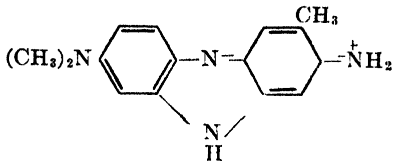
Azines



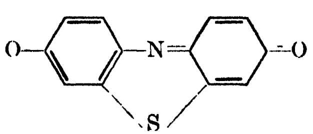
Safranine



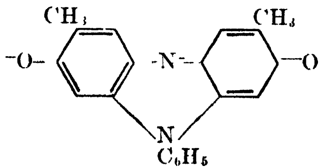
Methylene blue



Neutral red



Thionol or hydıoxyphenylthiazone



Safranole

dyestuffs with some of the corresponding indamines.

phthalic acid, respectively. Both phthalonic and phthalic acids are obtainable from naphthalene.[21]

5-*Aminophthalhydrazide*, or 5-aminophthalaz-1,4-dione, is known also as "Luminol"[22] because of the striking bluish luminescence—one of the best known—which it displays when in dilute alkaline peroxide solution, potassium ferricyanide, or other oxidizing medium. The compound is prepared from 3-nitrophthalic acid and hydrazine sulfate under the condensing influence of sodium acetate followed by reduction of the nitro group with ammonium sulfide. A large number of related compounds have been tested for their luminescent power and for the color of light emitted. All compounds containing an unsubstituted cyclohydrazide ring attached to a benzene ring are chemiluminescent. In general, however, the 5-amino compound gives the strongest effect, particularly at 18° in the presence of hemoglobin as a catalyst.[23]

PYRIMIDINES

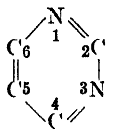
Compounds with a pyrimidine nucleus comprise by far the largest number of important members of the azine group. Monocyclic compounds are known as pyrimidines, a fused pyrimidine-imidazole system is known as a purine, and the fused benzene-pyrimidine system is known as quinazoline. The respective formulas are shown below.

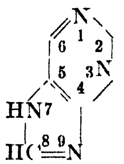
---

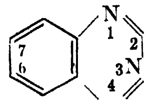
[21] Gabriel and Perkin, *Ber.*, **26**, 2210 (1893); *cf.* Ullmann and Uzbachian, *ibid.*, **36**, 1797 (1903).

[22] Huntress, Stanley, and Parker, *J. Am. Chem. Soc.*, **56**, 241 (1934); *J. Chem. Education*, **11**, 142 (1934).

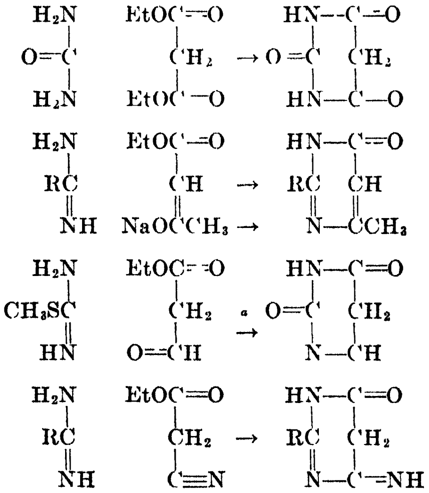
[23] Drew and Pearman, *J. Chem. Soc.*, 586 (1937); Drew and Garwood, *ibid.*, 836 (1939).







The common method of preparation is by condensation of a diamino or amino-imino compound with a dicarboxylic ester or its equivalent. The mono-, di-, or tri-keto product can then be converted to a chloro-substituted product by phosphorus oxychloride, and the latter group then eliminated by a conventional reduction. The four illustrations of the formation of a monocyclic ring system shown below are typical and show the use of urea, amidines, and pseudothiourea, with alkyl malonates, acetoacetates, formyl acetates, and cyano acetates as common intermediates.



[a] Hydrolysis of the intermediate mercapto (CH_3S—) product occurs.

In such manner, and by subsequent conversion to chloride and reduction, pyrimidine (m.p. 21°, b.p. 134°) is obtained from urea and methyl malonate[24] or from methylpseudothiourea and ethyl formylacetate;[25] the 2-methyl[26] homologue (m.p. −4°, b.p. 138°/758 mm.) is prepared from acetamidine and ethyl formylacetate; the 4-methyl[27] compound (m.p.

[24] Gabriel, *Ber.*, **33**, 3666 (1900).

[25] Wheeler and Merrian, *Am. Chem. J.*, **29**, 478 (1903).

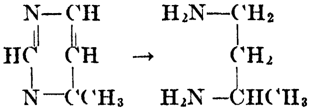
[26] Gabriel, *Ber.*, **37**, 3639 (1904).

[27] Behrend, *Ann.*, **229**, 1 (1885).

$< -150°$, b.p. 142°/762 mm.) is made from urea and ethyl acetoacetate; the 5-methylpyrimidine[28] (m.p. 30.5°, b.p. 151.5°/735 mm.) is synthesized from urea and ethyl isosuccinate; the 2,4-dimethyl[29] homologue (m.p. −7°, b.p. 146°) is prepared from acetamidine and ethyl acetoacetate; the 4,5-dimethyl compound (m.p. 3°, b.p. 177°) is made from ethyl pseudothiourea[25] and ethyl methylacetoacetate or from guanidine carbonate and the same ester[30]); the 4,6-dimethylpyrimidine (m.p. 25°, b.p. 195°/768 mm.) is obtained from urea and acetylacetone[31] or from methylpseudothiourea and acetylacetone[32]); and 4-methyl-5-ethylpyrimidine[25] (m.p. 238°d.) is made from methylpseudothiourea and ethyl ethylacetoacetate. Aryl homologues are prepared by similar reactions which employ arylamidines or other intermediates with a benzene ring. Benzamidine and ethyl acetoacetate, for example, give 2-phenyl-4-methylpyrimidine after the phosphorus oxychloride–zinc and water treatment of the 6-keto product.

These compounds, in general, are miscible or appreciably soluble in water, depending on the alkyl groups present. They are neutral to litmus and form double salts with mercuric chloride.

Reduction with sodium and boiling absolute alcohol opens the ring and forms a saturated diamino compound.[33] The process is another illustration of the formation of aliphatic from heterocyclic compounds.



Permanganate oxidation[34] converts the alkyl side chains to carboxylic acids. Benzaldehyde and zinc chloride forms a benzylidene derivative when the methyl substituent is flanked by an amonoaldehyde group in the ring.

The chloro compounds derived from the oxo intermediates in the above preparations show the typical behavior when adjacent to a C=N group. Ammonolysis occurs at 150 to 200°. If two or more halogens are present in the same molecule, an adjustment in temperature will usually permit one or the other to be favored in this replacement reaction.

Potassium thiocyanate similarly effects a replacement[35] of a chloro atom by a thiocyanate group as shown by partial formulas below.

---

[28] Gerngross, *Ber.*, **38**, 3394 (1905).

[29] Pinner, *ibid.*, **22**, 1612 (1889).

[30] Schlenker, *ibid.*, **34**, 2812 (1901).

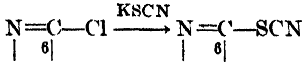
[31] Angerstein, *ibid.*, **34**, 3956 (1901).

[32] Wheeler and Jamieson, *Am. Chem. J.*, **32**, 342 (1906).

[33] Byk, *Ber.*, **36**, 1924 (1903).

[34] Gabriel and Colman, *ibid.*, **32**, 1537 (1899); **33**, 3667 (1900).

[35] Johnson and Süto-Nagy, *J. Am. Chem. Soc.*, **63**, 261 (1941).



$$N{=}C{-}Cl \xrightarrow{KSCN} N{=}C{-}SCN$$

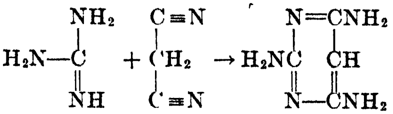
The method below used so successfully for transforming a thiocyanate

$$RSCN + 3Cl_2 + H_2O \rightarrow RSO_2Cl + 4HCl + CNCl$$

to a sulfonyl chloride does not work satisfactorily with this thiocyanate. A welter of related chemical compounds results, probably caused by the fact that the by-product, cyanogen chloride, which readily attacks pyridine systems, attacks the pyrimidine system also.

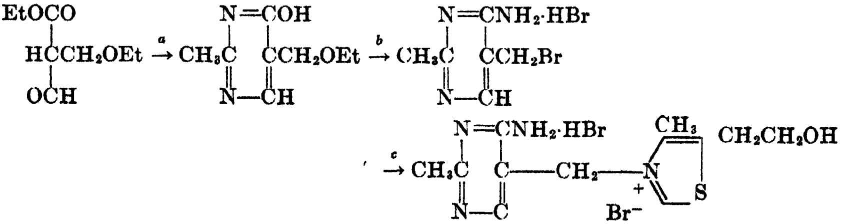
Sulfadiazine is the product of the reaction of *p*-aminobenzenesulfonyl chloride with 2-aminopyrimidine. The compound is a member of the valuable sulfa-drug series.

Triaminopyrimidine is obtained either from the reaction of 2,4,6-trichloropyrimidine[36] and alcoholic ammonia at 215° or from guanidine and malonitrile.[37]



2-Methyl-6-amino-5-bromomethylpyrimidine.—This compound is one of the components of vitamin B. Cleavage of the vitamin by liquid ammonia gives $C_6H_{10}N_4$, with bisulfite gives $C_6H_9N_3SO_3$ and C_6H_9NSO. The absorption spectrum of $C_6H_{10}N_4$ is different from the bands of 2,6-2,4-, or 5,6-diaminopyrimidine, but is similar to those of 5-alkyl-6-aminopyrimidine. Sodium in liquid ammonia converts $C_6H_{10}N_4$ to $C_6H_9N_3$, which is identical with 2,5-dimethyl-6-aminopyrimidine.

Synthesis[38] of the pyrimidine half of vitamin B_1 and thence the vitamin (thiamin) itself is accomplished by the sequence of reactions pictured below.



[a] The starting material is prepared by the condensation of ethyl β-ethoxypropionate and ethyl formate under the influence of sodium ethoxide. This aldehydo ester then condenses with acetamidine.
[b] $POCl_3$, alc. NH_3, HBr. [c] Salt formation with 4-methyl-5-(β-hydroxyethyl)-thiozole (see p. 428).

---

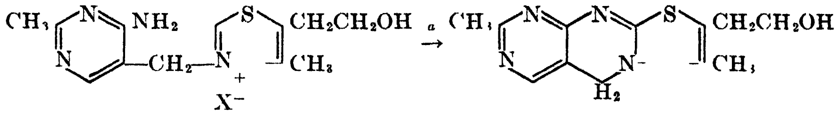
[36] Gabriel, *Ber.*, **34**, 3363 (1901); **38**, 149 (1905).

[37] Traube, *ibid.*, **37**, 4545 (1904).

[38] Williams, *J. Am. Chem. Soc.*, **58**, 1063 (1936); **57**, 229 (1935); Williams and Cline, *ibid.*, **58**, 1504 (1936); Williams, Ruehle, and Finkelstein, *ibid.*, **59**, 526 (1937); William and Spies, "Vitamin B_1," The Macmillan Company, New York, 1938.

Thiamin (vitamin B_1) was first isolated in comparatively pure crystalline form in 1926 by Jensen and Donath, analyzed correctly in 1932 by Windaus, and synthesized[38] in 1936 by Williams and coworkers. A diet deficient in thiamin leads to beriberi. The disease was particularly prevalent in the Philippines, Dutch East Indies, China, and Japan, where the inhabitants subsist largely on polished rice. Wheat germ, yeast, and rice polishings are good sources of thiamin.

Thiamin is oxidized by potassium ferricyanide to thiochrome (m.p. 226 to 227°). The intensity of the violet-blue fluorescence of this product under ultraviolet light measures the amount of thiamin present in a sample.[39]



^{a} K_3FeCN_6

Barbituric Acid and the Barbiturates.– 2,4,6-Trioxypyrimidines are known as barbiturates, after barbituric acid, the parent member of the series, itself prepared by the condensation of urea with a malonic ester under the influence of sodium alkoxide or phosphorus oxychloride.[40]

Barbituric acid has an active methylene between two carbonyl groups and an acid function. The chemical properties accord with expectations. Benzaldehyde forms the 5-benzal derivative, nitrous acid yields a nitroso product[41] called violuric acid, phenyldiazonium chloride forms the hydrazone of alloxan,[42] urea at 150 to 170° yields the 5-carbonic amide compound[43] known as malobiuret or pseudouric acid, fuming nitric acid converts it to the 5-nitro product,[41,44] sometimes called dilituric acid, and bromine yields a 5,5-dibromo product,[44] otherwise called dibromin.

Phosphorus oxychloride at 130 to 140° converts barbituric acid to a trichloro compound, which, in turn, with alcoholic ammonia gives, at 100°, a mixture of the 2- and 6-amino products, at 160°, the 2,6-diamino-4-chloro compound, and at 300°, the 2,4,6-triaminopyrimidine.

The acidity of barbituric acid is related to the active methylene group between two carbonyl groups, the symmetrical and conjugated ring system of the enolic form, and the comparatively stable imino carboxylic acid which is a resonance hybrid of more than one electronic state. No one factor is sufficient. Ethyl malonate, with an active methylene group, has low acidity; phloroglucinol has the symmetrical and conjugated unsaturated ring system but is comparatively weak; and amides have a potential imino carboxylic acid system but have no factor that will create stability to such an arrangement. The resultant of these influences is the strong carboxylic acid character of barbituric acid, stronger even than acetic or benzoic acid. The series below shows these comparisons in detail. Heavy lines emphasize the imino carboxylic acid group which is part of the ring structure. Some corresponding parts in the other molecules mentioned are shown by heavy lines also.

---

[39] Barger, Bergel, and Todd, *Ber.*, **68**, 2257 (1935); Jansen, *Rec. trav. chim.*, **55**, 1046 (1936); Hennessy and Cerecedo, *J. Am. Chem. Soc.*, **61**, 179 (1939).

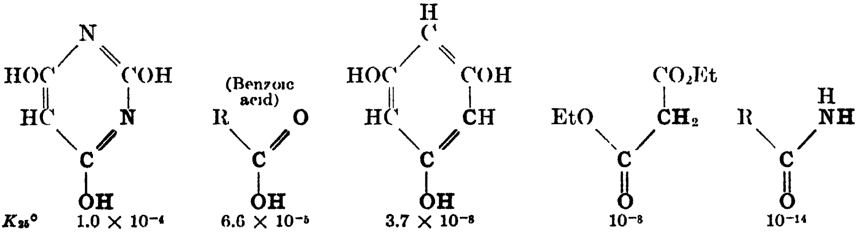
[40] Dickey and Gray, *Org. Syntheses, Coll. Vol.* II, 60 (1943).

[41] Baeyer, *Ann.*, **130**, 129 (1864).

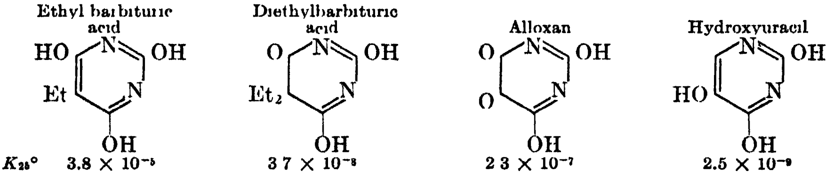
[42] Kühlung, *Ber.*, **31**, 1973 (1898).

[43] Baeyer, *Ann.*, **135**, 312 (1865).

[44] Hartman and Sheppard, *Org. Syntheses*, **12**, 58 (1932).



Changes and substitution that destroy one of these factors may have a marked effect on the acidity. Monosubstituted barbituric acids show a slight difference only in acidity, but 5,5-disubstituted acids show a marked drop. Alloxan cannot attain a conjugated ring structure, and hydroxyuracil lacks symmetry. These compounds lack the acidity[45] of barbituric acid.

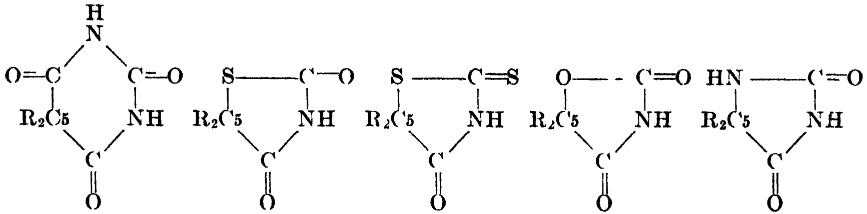


The comparative effect[46] of dialkylation in barbituric acid and the azolones is shown below. The azolones lack the essential features that characterize barbituric acid. Hence dialkyl substitution has little effect on the acidity of the azolones, but has a great effect on that of barbituric acid. Obviously, the hydrogen atoms on carbon scarcely participate in any acidity that the azolones possess.

---

[45] Wood, *J. Chem. Soc.*, **89**, 1831 (1906).

[46] Erlenmeyer and Kleiber, *Helv. Chim. Acta*, **22**, 851 (1939).



pH values					
R_2—H_2	4 98	6 77	5 77	5 84	9 12
R_2—$(CH_3)_2$	7 14	6 64	5 38	6 11	9 19

Methylation[47] of barbituric acid by the silver salt and methyl iodide method gives the N-methyl derivative, by diazomethane gives both mono and di N-methyl ethers.[48] The acid is converted to an insoluble powder, $C_6H_4O_3N_4$, by the action of cyanogen.[49]

The barbiturates are known chiefly for their hypnotic and sedative action, which was discovered[50] in 1803. The number of compounds that have been studied is now so large that general rules[51] can be formulated for predicting the effect. For good action the compound must be dialkylated at C_5. The two alkyl groups should have from four to eight carbon atoms. One alkyl group must be of the open-chain type. The hypnotic effect decreases if the molecular weight is greater than 250. Alkylation of the nitrogen atom causes an antiepileptic effect.

The drugs are not known to undergo any chemical reaction in the living cell, but are believed to reduce the permeability of the nerve cell by surface adsorption. Metabolism is thus curbed; sleep is induced. The effect,[52] according to the Overton-Meyer theory (1899), is determined by the distribution of the drug between the blood and the nerve cells which are rich in lipoids.

$$\text{Distribution coefficient} = \frac{\text{lipoid solubility}}{\text{water solubility}}$$

The drug is generally administered in conjunction with various others, particularly the analgesics and antipyretics, in order to enhance the effectiveness. Since many of these other drugs are basic, they will form molecular complexes with the barbiturate.[53] A few of the common barbiturates are listed in Table I, in the order of increasing size of one of the alkyl substituents in the 5,5-disubstituted compound, followed by the thio- and the tri-substituted products.

---

[47] CONRAD and GUTHZEIT, *Ber.*, **14**, 1643 (1881); **15**, 2848 (1882).

[48] DOX, *J. Am. Chem. Soc.*, **58**, 1633 (1936).

[49] NENCKI, *Ber.*, **5**, 886 (1872).

[50] FISCHER and v. MERING, *Chem. Zent.*, **74**, I, 1155 (1903).

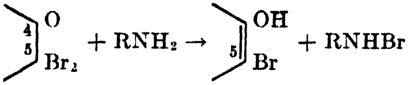
[51] DOX, *J. Am. Chem. Soc*, **45**, 1811 (1923).

[52] QUASTEL, *Trans. Faraday Soc.*, **39**, 348 (1943).

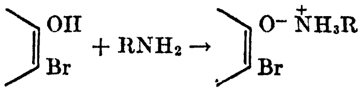
[53] KUHN and RICHTER, *J. Am. Chem. Soc.*, **57**, 1927 (1935).

5-Nitrobarbituric acid, or dilituric acid, is made by nitration of barbituric acid.[54] It melts at 176° d. The compound has some interest in analytical chemistry as a reagent for the separation of sodium from potassium compounds.[55]

Dibromobarbituric acid (Dibromin) is obtained readily by bromination of barbituric acid. The two bromine atoms do not react with equal ease. In keeping with the general properties of persubstituted halogen compounds, it can act as an oxidizing agent. Ammonia and primary and secondary amines remove one halogen atom and form an ammonium salt,[56] according to the partial formulas below.

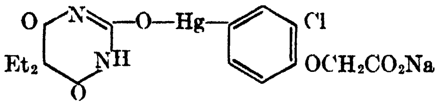


$$2RNHBr + C_2H_5OH \rightarrow 2RNH_2 + CH_3CHO + Br_2$$

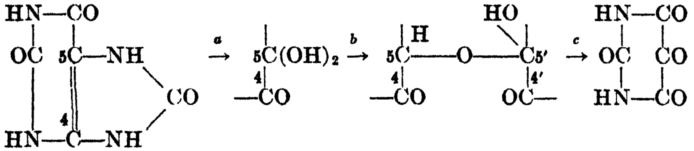


If the amine is aniline, one of the products is *p*-bromoaniline.

Merbaphan, sometimes known as "Novasural" is the double salt of sodium hydroxymercurichlorophenoxyacetate and diethylbarbituric acid. The drug is a powerful diuretic. A glance at the formula shows that it is obviously a product of the interaction of a barbiturate with a mercurated chlorophenol derivative.



Alloxan (m.p. 254° d.) is conveniently prepared[57] by oxidation of uric acid or alloxantin by nitric acid or by chromic acid oxidation of benzalbarbituric acid.



Uric acid Alloxantin Alloxan

[a] KClO₃, HCl. [b] H₂S. [c] HNO₃.

---

[54] Hartman and Sheppard, *Org. Syntheses, Coll. Vol.* II, 440 (1943).

[55] Derner and Derner, *J. Am. Chem. Soc.*, **61**, 3302 (1939); Plein and Dewey, *Ind. Eng. Chem., Anal. Ed.*, **15**, 534 (1943).

[56] Cope, *J. Am. Chem. Soc.*, **54**, 1251 (1932); Nightingale and Morris, *ibid.*, **58**, 1469 (1936).

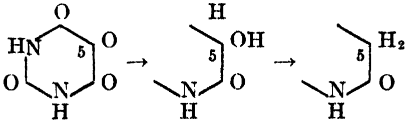
[57] Hartman and Sheppard, *Org. Syntheses*, **23**, 3 (1943); Speer and Dabovich, *ibid.*, **21**, 5 (1941).

TABLE I

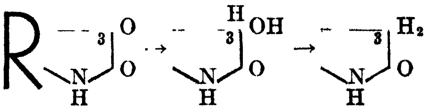
Barbituric Acid Substituents	Common Name
Methyl phenyl	Rutonal
Diethyl	Barbital or Veronal
Ethyl isopropyl	Ipral
Ethyl *n*-butyl	Neonal
Ethyl isoamyl	Amytal
Ethyl α-methylbutyl	Pentobarbital, Nembutal, or Embutal
Ethyl *n*-hexyl	Ortal
Ethyl phenyl	Phenobarbital or Luminal
Ethyl cyclohexyl	Phanodorn
Ethyl 1-piperidyl	Eldoral
Di-*n*-propyl	Proponal
Isopropyl allyl	Allonal or Numal
Isopropyl β-bromoallyl	Nostral or Noctal
Isobutyl allyl	Sandoptal
sec-Butyl β-bromoallyl	Pernocton
α-Methylbutyl β-bromoallyl	Rectidon
Diallyl	Dial
Ethyl α-methylbutyl thio[a]	Pentothal
Methyl cyclohexyl N-methyl	Evipal
Ethyl phenyl N-methyl	Prominal
Isopropyl β-bromoallyl N-methyl	Eunarcon

[a] Thiobarbituric acid derivative.

Alloxan has a historical interest in that Baeyer, early in his work on indigo, was led to some conclusions as to the structure of isatin from the similarity to alloxan. The resemblance is shown below with partial formulas.



Alloxan Dialuric acid Barbituric acid



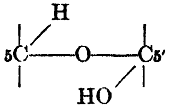
Isatin Dioxindole Oxindole

The above comparison suggests that the 5-keto group in alloxan will participate in the same reactions as does the 3-keto group in isatin. It is, indeed, sufficiently active to condense with benzene in the presence of sulfuric acid to form 5,5-diphenylbarbituric acid in the same way that isatin yields phenolisatin.[58]

Alloxan acts as a hydrogen acceptor with many compounds such as absolute alcohol in sunlight, hydrazobenzene, indigo white, hydrouracil, and α-amino acids. The last lose ammonia and carbon monoxide while undergoing conversion to aldehydes.[59] The alloxan meanwhile is reduced to alloxantin,

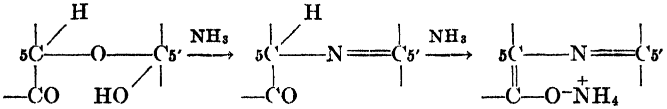
---

[58] McElvain, *J. Am. Chem. Soc.*, **57**, 1301 (1935).



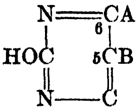
by a bimolecular change at the 5-keto group.

Purpuric acid and murexide. Treatment of alloxantin with dry ammonia in boiling absolute ethanol gives murexide, which is the acid ammonium salt of purpuric acid.[60] The chemical changes in formation of purpuric acid and murexide occur at the 5,5′ link as shown below.



The crystals of murexide have a green metallic luster. In aqueous solution, purpuric acid hydrolyzes slowly to uramil and alloxan.

Cytosine, Uracil, 5-Methylcytosine.—These compounds are present in nucleic acid, from which they are obtained by hydrolysis. Each contains a hydroxy group in the 2-position and a hydroxy or amino group in the 6-position. 5-Methylcytosine has, in addition, a methyl group in the 5-position. These relationships are made evident by the structural formula below.



Substituent at A	Substituent at B	Name	M.p., °C.
OH	H	Uracil	338°
NH_2	H	Cytosine	
NH_2	CH_3	5-Methylcytosine	

Uracil is prepared from urea and ethyl formylacetate.[61] Catalytic reduction of uracil over platinum gives hydrouracil by saturation of the 4,5-double bond. Uracil can be restored (*a*) by treatment with alloxan which serves as a hydrogen acceptor or (*b*) by bromination followed by thermal elimination of hydrogen bromide above the melting point (195°) of the 5-bromohydrouracil or by alkali and pyridine treatment.

Cytosine is a hydrolysis cleavage product of thymus nucleic acid and is widely distributed in nature, as, for example, in the wheat embryo and in yeast cells. In the laboratory, it is prepared from ethyl pseudothiourea and ethyl formylacetate, followed by the chlorination ($POCl_3$)

---

[59] Brown and Johnson, *ibid.*, **45**, 2702 (1923); Johnson, *ibid.*, **63**, 263 (1941).

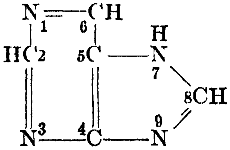
[60] Hartley, *J. Chem. Soc.*, **87**, 1791, 1796 (1905); Hantsch and Robinson, *Ber.*, **43**, 92 (1910).

[61] Johnson, *J. Am. Chem. Soc.*, **63**, 263 (1941).

and ammonia treatment, in order to install the 6-amino group, and hydrolysis with hydrogen chloride, to replace the 2-methylmercapto by a hydroxy group. It can be made, also, from uracil by conversion to the dichloride, ammonolysis of the 2,6-dichloropyrimidine by alcoholic ammonia at 100°, separation of the two isomeric chloroamino products (2-amino-6-chloropyrimidine is volatile in steam), treatment of the 2-chloro-6-aminopyrimidine with sodium methoxide, and hydrolysis of the ether with aqueous hydrochloric acid.

5-Methylcytosine has been obtained from tuberculinic acid prepared from desiccated tubercle bacilli grown in beef broth.[62] The acid is hydrolyzed by 25 per cent sulfuric acid and the 5-methylcytosine separated, together with cytosine and thymine.

Purines.- This series of compounds is widely distributed in nature as an important constituent in the nucleic acids, as alkaloids in popular beverages, as uric acid, and as a component of certain enzymes. The parent member of the series is obtained from uric acid by the customary conversion of all hydroxy to chloro groups, followed by elimination of the halogen by reduction. Purine melts at 217°. As expected from the large number of ammonoaldehyde groups that are present, the compound is readily soluble in water and insoluble in ether. The formula is shown below. When purine compounds are attached to sugars, as nucleosides, the position of joining is at N_7 or N_9.



Some naturally occurring purines are listed in Table II. These compounds have an oxygen atom at C_6, except adenine, which has an amino group. These purine bases and uric acid have no methyl groups. Hence the keto groups can exist in the tautomeric hydroxy form, as indicated in the table. The three alkaloids have a methyl group at N_3, which would retard enolization with the keto group at C_2. Caffeine, which is the most powerful alkaloid, has methyl groups at three nitrogen atoms; theophylline, which is the next most powerful, has methyl groups on two nitrogen atoms so that enolization to the hydroxy compound is impossible; theobromine, which is benign in action, has methyl groups on two nitrogen atoms, but has one keto group which can undergo the change to the tautomeric form. The alkaloids are N-ethers and hence have melting instead of decomposition points; of the three compounds, the trimethyl product, caffeine, has the lowest melting point.

---

[62] Johnson and Coghill, *ibid.*, **47**, 2838 (1925).

The structural differences between the most widely used sleep-inducing drugs, the barbiturates, and the most widely used sleep-destroying drugs, caffeine and theophylline, provide an interesting subject for reflection. Both have a pyrimidine base. The former have two alkyl groups at C_5 and can undergo tautomerism readily. The latter has an N-methyl urea system attached to the pyrimidine ring at C_5 and also at C_4 and has methyl groups at N_1 and N_3 so that no enolization can take place. Theobromine, which is the only one of these alkaloids that can undergo tautomerization, has little stimulating influence.

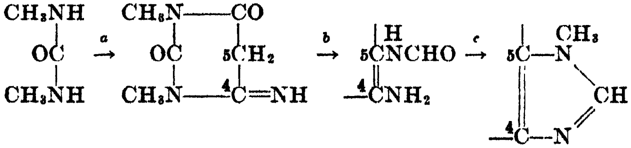
TABLE II.—NATURAL PURINE COMPOUNDS

	Substituent in positions						M.p., °C
	1	2	3	6	7	8	
Nucleic acid bases:[a]							
Adenine	. . .	. . .	. . .	NH_2			360–365
Hypoxanthine	. . .	. . .	. . .	OH	. . .	. . . .	d.
Guanine	. . .	NH_2	. . .	OH	. . .	. . . .	d.
Xanthine	. . .	OH	. . .	OH	. . .	. . . .	d.
Alkaloids:							
Theophylline	CH_3	=O	CH_3	=O	. . .	. . . .	269–272
Theobromine	. . .	=O	CH_3	—OH	CH_3	. . . .	337
Caffeine	CH_3	=O	CH_3	=O	CH_3	. . . .	235–237
Acids:							
Uric acid	. . .	OH	. . .	—OH	. . .	—OH	d.

[a] The keto forms of the bases are known by the prefix *iso-*, *e.g.*, isoxanthine.

Coffee contains caffeine, tea contains caffeine and theophylline, and cocoa contains theobromine. Soft drinks such as cola contain caffeine; so does maté, a common drink in many parts of South America. The kola nut in the Sudan contains 2 per cent of caffeine. Caffeine is a powerful stimulant of the central nervous system.[63] Approximately 100 to 150 mg., a therapeutic dose, is in each cup of coffee; and a similar amount is in each cup of tea. Children are more susceptible than adults to caffeine, but are unaffected by the theobromine in cocoa. Caffeine can be removed from coffee by extraction.

The synthesis[64] of *caffeine*, shown below, is typical of the chemistry in this series.



[a] Condensation with cyanoacetic acid, ring closure by use of KOH which forms the imide. [b] HNO_2, reduction to the amine, formic acid. [c] Treatment of the formyl compound with CH_3I and alkali.

---

[63] GOODMAN and GILMAN, "The Pharmacological Basis of Therapeutics," The Macmillan Company, New York, 1941.

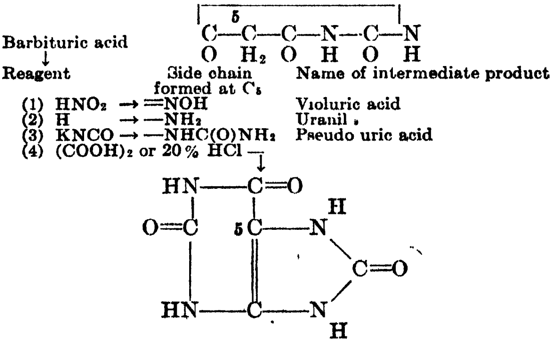
[64] FISCHER, *Ber.*, **30**, 559 (1897).

Theophylline is converted to caffeine by use of the silver salt and methyl iodide.[65] By a similar reaction, nucleosides can be prepared from the silver salt and such derivatives as acetobromogalactose or arabinose followed by hydrolysis with alcoholic ammonia.[66]

Uric acid is one of the early known compounds in organic chemistry, having been isolated in 1776 by Scheele and von Bergmann from the bladder. It is present in small quantities in urine and, as the ammonium salt, is the principal component of the excrement of birds, reptiles, and insects. Abnormal pathological conditions in man cause the deposition of the comparatively insoluble monosodium salt (the disodium salt is soluble) in the joints, the disease being known as gout.

Though isolated in 1776, the correct structure was not deduced until nearly a hundred years later when von Medicus[67] skillfully arranged a formula that accounted for the degradation fragments then known, *viz.*, (*a*) glycine, carbon dioxide, and ammonia by the action of fuming hydrochloric acid or hydriodic acid; (*b*) urea and alloxan (known to be derivable from mesoxalic acid and urea) by oxidation with nitric acid or chlorine; (*c*) parabamic acid [oxalylurea, C(O)C(O)NHC(O)NH] and carbon dioxide, both derived by further oxidation of alloxan; and (4) allantoin by oxidation with lead peroxide, potassium ferricyanide, or potassium permanganate.

A synthesis, which confirmed this deduction, was carried as far as the pseudo acid stage by Baeyer in 1863 and completed by Fischer in 1895 with the discovery of a successful reagent (quick heating with oxalic acid[68] at 145 to 155° for 10 min. or with 20 per cent hydrochloric acid[69] for 20 min.) for closing the ring. In the steps shown below, the branch begins at C_5 in the pyrimidine ring and ring closure takes place at C_4.



---

[65] Kossel, *Z. physiol. Chem.*, **13**, 304 (1889); Helferich and Kühlewein, *Ber.*, **53**, 17 (1920).

[66] Pryde and Williams, *J. Chem. Soc.*, 640 (1933).

[67] v. Medicus, *Ann.*, **175**, 243 (1875). See also Fischer, *Ber.*, **17**, 1776 (1884).

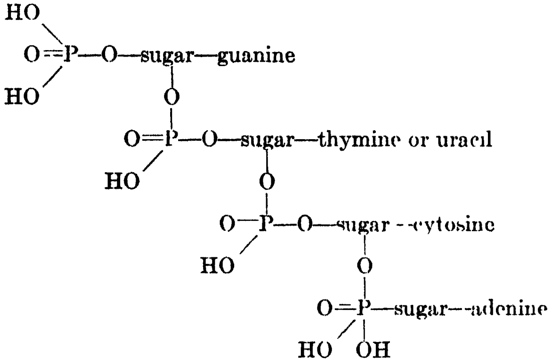
[68] Fischer and Och, *ibid.*, **28**, 2473 (1895).

[69] Fischer, *ibid.*, **30**, 559 (1897).

Uric acid decomposes without melting above 400°. It is a weaker acid than acetic, the dissociation constant being of the order of 10^{-6}. It is scarcely soluble in water.

Phosphorus oxychloride at 130 to 140° converts uric acid to 2,6,8-trichloropurine; wet chlorine, bromine, or oxidizing agents change the acid to alloxan; and methyl iodide and alkali convert it to the 1,3,7-trimethyl ether.

Nucleic acids are colorless amorphous powders that are obtained by mild hydrolysis of cellular material.[70] Yeast contains an acid in the free state, about 4 to 7.5 g. of acid per kilogram; the thymus and pancreas contain one as a nuclear protein from which it is liberated by enzymic or mild chemical hydrolysis. More vigorous hydrolysis breaks an acid into sugars, phosphoric acid, pyrimidines, and purines. A probable configuration is shown below.



The pentose sugars, *l*-ribose and *d*-arabinose, are present. The hexoses, *l*-glucose and α-methylthioketopentose, occur among the naturally occurring nucleosides.

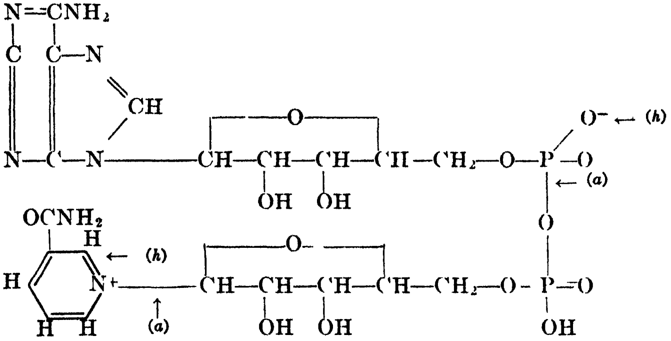
The early classification of nucleic acids as of plant and animal origin is now regarded as inadequate and has been replaced by one based on the sugar present. For example, thymonucleic acid, of animal origin, is called a desoxyribonucleic acid from thymus, and yeast nucleic acid of plant origin is called a ribonucleic acid from yeast.

Physiologically, the nucleic acids[63] appear to influence the white blood cell count of animals. The hydrolysis products xanthine, guanine, and adenine also produce a rise in leukocyte values.

Codehydrogenase I contains adenine and is known as a diphosphopyridine nucleotide. Its function is to remove hydrogen from a molecule, so that oxygen, otherwise supplied, may combine. The probable structure[71] is shown below.

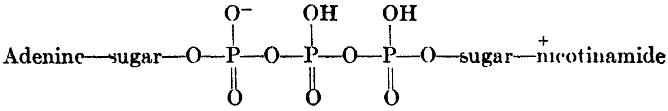
---

[70] Levene and Bass, Nucleic Acids, American Chemical Society Monograph Series 56; Johnson and Hahn, *Chem. Rev.*, **13**, 196 (1933); Allen, *Ann. Rev. Biochem.*, **10**, 221 (1941); Gulland, *J. Chem. Soc.*, 1722 (1938).



The compound dissolves readily in water and is stable at 80°. Alkaline hydrolysis breaks the molecule at the points marked (*a*). The specific dehydrogenation action destroys the inner saltlike character of the molecule and converts the pyridine ring to a dihydropyridine compound. Addition of hydrogen takes place at the points marked (*h*).

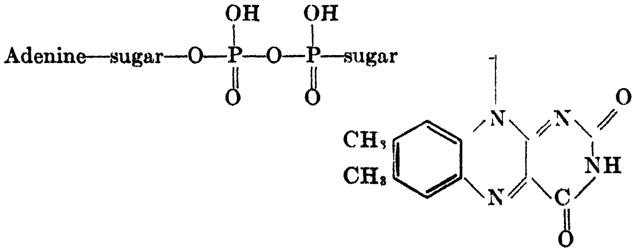
Codehydrogenase II, once known as Warburg's ferment, has a structure similar to that of codehydrogenase I, save for the fact that it is a triphosphopyridine, instead of a diphosphopyridine nucleotide.[72] The extra phosphoric acid unit is inserted between the two present in the diphospho compound.



$$\text{Adenine—sugar—O—}\underset{\parallel}{\overset{\text{O}^-}{\text{P}}}\text{—O—}\underset{\parallel}{\overset{\text{OH}}{\text{P}}}\text{—O—}\underset{\parallel}{\overset{\text{OH}}{\text{P}}}\text{—O—sugar—}\overset{+}{\text{nicotinamide}}$$

An enzyme converts the tri- to the di-compound. The chemical actions of the two compounds are similar.

Alloxazine-adenine-dinucleotide is believed to have a structure similar to those pictured for codehydrogenase except that the dihydropyridine end is replaced by an alloxazine.



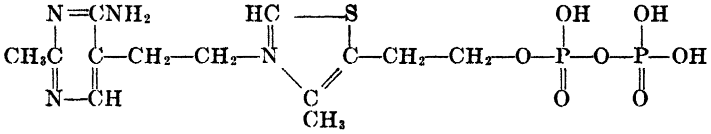
---

[71] Euler and Schlenk, *Z. physiol. Chem.*, **246**, 64 (1937).

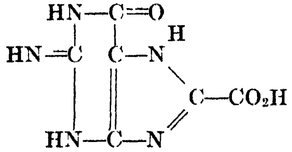
[72] Bell, *Science*, **88**, 131 (1938); *J. Biol. Chem.*, **128**, 51 (1939); Warburg and Christian, *Biochem. Z.*, **298**, 150 (1938); see also Allen, Ref. 70.

The compound acts as a coenzyme of *d*-amino acid oxidase. It has been isolated from milk, yeast, kidney, and liver.

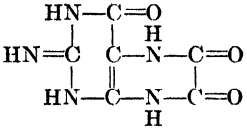
Cocarboxylase has been isolated from brewers' yeast and is necessary for the activity of carboxylase, pyruvic dehydrogenase, α-ketoglutaric carboxylase, and other enzymes. It is a combination of one thiamine with two phosphoric acids, one of which is more resistant to hydrolysis than the other.



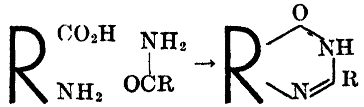
Pterins.—These pyrimidine compounds[73] are found as pigments in butterflies, wasps, and other insects. Leucopterin has been prepared by fusion of 2,4,5-triamino-6-hydroxypyrimidine with oxalic acid. The formula is either that of a purine or a fused pyrimidine-pyrazine system. The compounds are very difficult to purify.



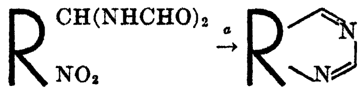
or



Quinazolines.—A few examples of the preparation of benzopyrimidine systems are shown below. The Niementowski reaction[74] involves the condensation of an amide with anthanilic acid or related compound. Diarylformamidines, acetamidines, and nitriles (with acetic anhydride) can be used in place of the acid amide, and acyl aminobenzamides can be



used in place of the anthranilic acid. Riedel's synthesis[75,76] consists of the reduction of *o*-nitrobenzaldiformamide with zinc dust and acetic acid. In general, the reduction of acyl derivatives of *o*-nitrobenzylamines gives



[a] Zn + CH_3CO_2H.

---

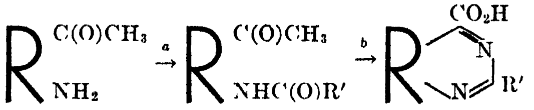
[73] WIELAND and PURRMANN, *Ann.*, **544,** 163 (1940); WIELAND, TARLTER, and PURMANN, *ibid.*, **545,** 209 (1940).

[74] MEYER and WAGNER, *J. Org. Chem.*, **8,** 239 (1943).

[75] PAAL and BENKER, *Ber.*, **32,** 1252 (1899).

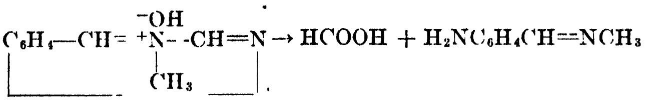
[76] BOGERT and MCCOLM, *J. Am. Chem. Soc.*, **49,** 2640 (1927).

amino compounds which by heat or distillation yield quinazolines. Another method, designed especially for the synthesis of analogues of cincophen, utilizes the readily available *o*-aminoacetophenone.[76]



[a] R′COCl + NaOH. [b] $KMnO_4$, NH_3 in CH_3OH at 110°.

The reactions[77] of the quinazolines are those predicted for a pyrimidine system which can be regarded also as a quinoline and isoquinoline combination. As in the case of pyrimidines, all keto products are readily transformed to the parent ring by a phosphorus oxychloride-reduction sequence. Catalytic (PtO) reduction of quinazoline gives the 3,4-dihydro compound, and subsequent sodium amalgam reduction gives 1,2,3,4-tetrahydroquinazoline. Permanganate then gives the 4-hydroxy compound as well as the 4,5-dicarboxylic acid of pyrimidine. Methyl iodide yields the 3-methiodide product, and pyrolysis of this salt with strong potassium hydroxide gives formic acid and *o*-aminobenzalmethyl amine.

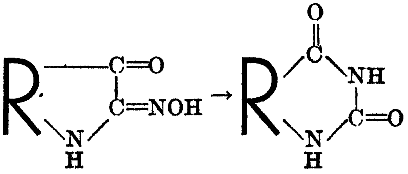


$$C_6H_4—CH=\underset{CH_3}{\overset{^{-}OH}{^{+}N}}-CH=N \rightarrow HCOOH + H_2NC_6H_4CH=NCH_3$$

Because of the similarity to quinoline and isoquinoline compounds and of the existence of quinazoline-containing alkaloids, there have been numerous studies of the physiological behavior of members of this series.

Quinazoline melts at 48° and boils at 243°. It is neutral and very soluble in water. With hydrochloric acid on a water bath, it loses ammonia slowly.

The 2,4-dihydroxy derivative, sometimes called benzoyleneurea, can be prepared by a Beckmann rearrangement of the α-oxime of isatin,[78] the latter obtained from O-methylisatin and hydroxyl amine.

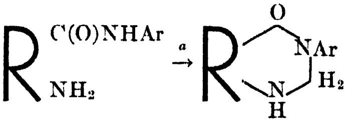


---

[77] Marr and Bogert, *ibid.*, **57**, 729 (1935); Gabriel, *Ber.*, **36**, 800 (1903); Gabriel and Colman, *ibid.*, **37**, 3643 (1904).

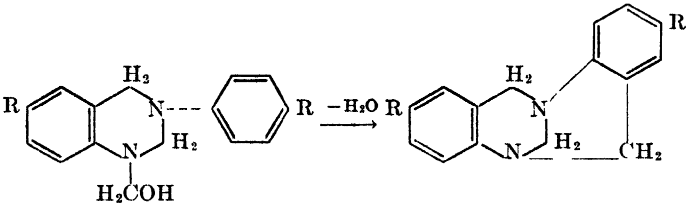
[78] Heller, *ibid.*, **49**, 2757 (1916).

3-Substituted 1,2,3,4-tetrahydroquinazolones are prepared from N-substituted anthranilanilide and formaldehyde or methylenediimines.[79] The compounds have a structure resembling that of the isoflavanones.



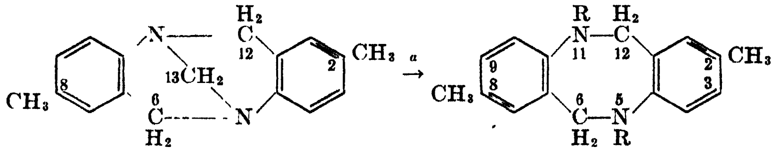
a H_2CO at 60° or $H_2C(NHR)_2$.

When the same synthesis is tried with an o-aminobenzyl aryl amine, the corresponding product is formed as an intermediate.' The final compound[80] is, however, a 1-methylol substituted quinazoline or a tetracyclic product in which a methylene bridge is formed. The tetracylic product is known as *Troger's base* from the original observation of



Final compound. R = Cl or Br. Final compound when R = CH_3, CH_3O, or C_2H_5O.

Troger[81] on the product of the action of p-toluidine with formaldehyde in acid solution. Troger's base (m.p. 135 to 136°) loses formaldehyde when acetylated or benzoylated. Nitrous acid gives a dinitroso product. Hydriodic acid converts it to 4-amino-1,3-xylene. The base can also be prepared by condensation of the tetrahydroquinazoline with formaldehyde in concentrated hydrochloric acid at 0°. These facts are consistent with the formula[82] below and its change to a phenhomazine by acetylation.



a RC(O)Cl.

Troger's base
2,8-Dimethyl-5,11-methano dibenzo[b,f][1,5]diazocine ("Ring Index" name)

R = $CH_3C(O)$— or $C_6H_5C(O)$—
2,8-dimethyl-5,11-diacylphenhomazine or 2,8-dimethyl-5,11-diacyl-dibenzo[b,f][1,5]diazocine ("The Ring Index")

The formation of Troger's base is the end result of a process,[83] the first step of which is the formation of a diimine or Schiff base which is unstable and rearranges to the aminobenzylaniline (or sometimes also to a diphenylmethane base). The aminobenzylaniline product then condenses with another molecule of formaldehyde or with the methylenediimine.

---

[79] Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

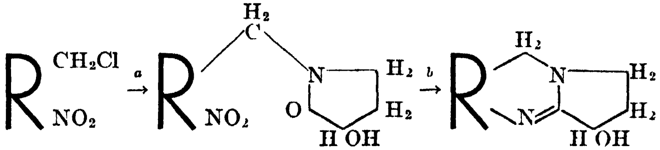
[80] Wagner and Eisner, *J. Am. Chem. Soc.*, **56**, 1938 (1934); Miller and Wagner, *ibid.*, **63**, 832 (1941).

[81] Troger, *J. prakt. Chem.* [2], **36**, 227 (1887).

[82] Spielman, *J. Am. Chem. Soc.*, **57**, 583 (1935).

[83] Wagner and Eisner, *ibid.*, **56**, 1938 (1934); Simons, *ibid.*, **59**, 518 (1937).

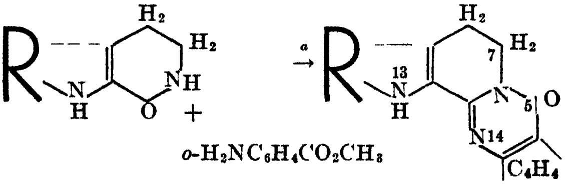
Vasicine (peganine) is an alkaloid present in a Himalayan plant, *Adhatoda vasica*, the extract from which is used in India as a fish poison, an insecticide, and for the relief of asthma. The alkaloid is associated also with the harmala alkaloids. Oxidation of vasicine gives quinazoloneacetic acid, which in turn with 20 per cent alcoholic potassium hydroxide gives anthranilic acid; treatment with phosphorus oxychloride followed by reduction with zinc and hydrochloric acid gives desoxyvasicine.[84] The last compound gives a benzal derivative[85] with benzaldehyde, a reaction that indicates an active methylene group adjacent to an ammono aldehyde. Vasicine is synthesized[86] by condensation of *o*-nitrobenzylchloride and γ-amino-α-hydroxybutyrate followed by reduction and spontaneous ring closure.



[a] $H_2NCH_2CH_2CH(OH)CO_2CH_3$. [b] $SnCl_2 + CH_3CO_2H + HCl$.

Desoxyvasicine can be obtained by a biogenic synthesis[87] from *o*-aminobenzaldehyde and the acetal of γ-aminobutyraldehyde, a process that suggests the origin of vasicine in nature.

Rutaecarpine and *evodiamine* are obtained from the dried fruit of *Evodia rutaecarpa*, used by the Chinese as a drug. The former is synthesized[88] by condensation of a ketotetrahydro-β-carboline with methyl anthranilate by means of phosphorus trichloride; the latter is prepared by a similar reaction with the N-methylanthranilate.



[a] PCl_5.

---

[84] Späth and Nikawitz, *Ber.*, **67**, 45 (1934).

[85] Hanford and Adams, *J. Am. Chem. Soc.*, **57**, 921 (1925).

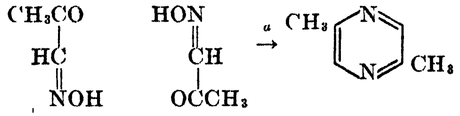
[86] Späth, *Ber.*, **68**, 407, 699 (1935).

[87] Schöpf and Oechler, *Ann.*, **523**, 1 (1936); *cf.* Robinson, *J. Chem. Soc.*, 1079 (1936).

[88] Asahina, Robinson, and Manske, *ibid.*, 1708 (1927).

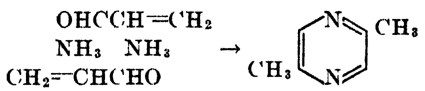
PYRAZINES

Pyrazines are obtained by the self-condensation of α-aminoaldehydes or ketones by the reaction illustrated below for the preparation of dimethylpyrazine from the isonitroso derivative of acetone.



a Sn + HCl.

The preparation of *β-alkylpyridines* by pyrolysis of glycerol and ammonium phosphate can be adapted to the synthesis of 2,5-dimethylpyrazine in good yield and of 2,5-dimethyl-3-ethylpyrazine by the introduction of more ammonia, in the form of ammonium chloride, in the reaction mixture.[89] The dimethylethylpyrazine comes presumably from the condensation of 2 molecules of acrolein, 1 of acetaldehyde, and 2 of ammonia.



A condensation of this general type is responsible for the formation of *fructosazine* (2,5-bis-tetrahydroxybutylpyrazine, $C_{12}H_{20}N_2O_8$) by the reaction of *d*-fructose with alcoholic ammonia.[90]

From these products, and related ones, it is possible to derive a variety of substituted pyrazines from reactions that are typical of pyridine-like systems. Oxidation of fructosazine with hydrogen peroxide and alkali or of 2,5-dimethylpyrazine with permanganate or of benzopyrazine (quinoxaline)[91] with permanganate gives a dicarboxylic acid. Decarboxylation gives pyrazine. Controlled oxidation, by diminished permanganate reagent, of 2,5-dimethylpyrazine gives 2-methylpyrazine-5-carboxylic acid which can be pyrolyzed to 2-methylpyrazine. Controlled decarboxylation, attained by pyrolysis at 2-3 mm., so that the mono carboxylic acid is removed by sublimation as rapidly as formed, converts pyrazine-2,3-dicarboxylic acid to pyrazine-2-carboxylic acid. The customary conversion of this carboxyl to an amine via the methyl ester, amide, and carbamate path is unique among Hofmann degradations in that an intermediate sodium pyrazinecarbamate, $C_5H_4N_3O_2Na$, can be isolated.[92] Mineral acids or acetic acid decompose the carbamate with effervescence to 2-aminopyrazine. Aminopyrazines can be prepared also by amination with sodium amide.[93]

---

[89] STOEHR, *Ber.*, **24**, 4105 (1891); *J. prakt. Chem.*, **51**, 449 (1895).

[90] DE BRUYN, *Rec. trav. Chim.*, **18**, 72 (1899); STOLTE, *C.A.*, **2**, 1978 (1908).

[91] GABRIEL and SON, *Ber.*, **40**, 4851 (1907); SAUSVILLE and SPOERRI, *J. Am. Chem. Soc.*, **63**, 3153 (1941).

[92] ITALL and SPOERRI, *J. Am. Chem. Soc.*, **62**, 664 (1940).

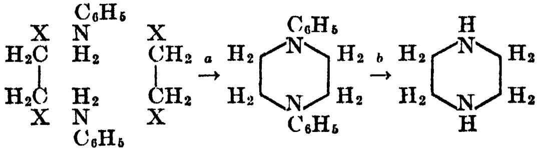
The parent member of the series, *pyrazine*, is the most symmetrical of the three diazines and, therefore, has the highest melting point, as shown below.

Common name	Diazine	B.p., °C.	M.p., °C.	Change in m.p., °C.
Pyridine	... .	115	−42	
Pyridazine	1,2-diazine	208	−8	34
Pyrimidine	1,3-diazine	124	22	30
Pyrazine	1,4-diazine	118	53	31

The increase in melting point as the second nitrogen is introduced into the pyridine ring in the positions listed above is approximately the same for each unit of distance from the first nitrogen atom.

Pyrazine is miscible with water in all proportions and is very soluble in alcohol and ether. It is a strong light-refracting liquid. Bromine yields an addition compound; and picric acid, chloroplatinic acid, mercuric salts, and other metal salts form complexes that are useful in identification.

Piperazines can be prepared by reduction of pyrazines. They can also be prepared by the reaction of amines and ethylene dihalide. By such a method, aniline gives N,N-diphenylpiperazine, which has the properties of a dimethylaniline. Hence nitrous acid converts this piperazine to a dinitroso compound, which undergoes hydrolysis, like *p*-nitrosodimethylaniline, and gives piperazine. Arylsulfonamides react with ethylene dibromide in the presence of alkali to give a sulfonylpiperazine compound which by hydrolysis gives piperazine. This type of reaction is general for the preparation of secondary amines. Reduction of amino acid anhydrides, such as occur in proteins, with sodium and boiling amyl alcohol or electrolytic reduction of diketopiperazines in general gives piperazines.[94]



[a] Heat. [b] HNO_2, NaOH.

$$2RSO_2NH_2 + 2BrCH_2CH_2Br \xrightarrow{NaOH} RSO_2N(CH_2CH_2)_2NSO_2R$$

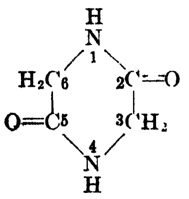
---

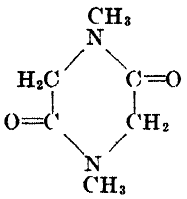
[93] JOINER and SPOERRI, *ibid.*, **63**, 1929 (1941).

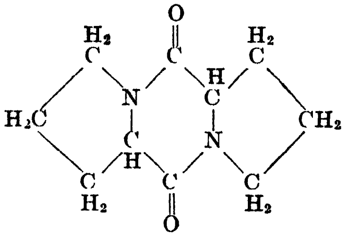
[94] WREDE, BRUSCH, and KEIL, *Z. physiol. chem.*, **200**, 133 (1931).

Piperazine (m.p. 104°, b.p. 146°) is a strong base and will absorb carbon dioxide from the air. Concentrated hydrochloric acid at 250° has no effect upon the ring system. It reacts readily with aldehydes[95] to form an N,N′-bispiperazylalkylmethane type of compound. Methylene iodide gives the same type of product as does formaldehyde, and benzal chloride gives the same type as benzaldehyde. Unless special precautions are taken, both ends of the piperazine molecule react. At pH of 2.8 to 4.6, one molecule of ethyl chloroformate reacts.[96] The remaining imino group can then be treated with ethylene oxide or other oxide. The ethyl formate radical can then be removed by hydrolysis.

2,5-*Diketopiperazines* are the product of a spontaneous change when the ethyl esters of α-amino acids are allowed to stand in alcohol solution or in a desiccator. The compounds are anhydrides and are frequently called by such names as glycine anhydride, sarcosine anhydride, proline anhydride (shown, respectively, below) depending on the amino acid from which they are derived.







They can be regarded also as double inner acid amides. The melting points are accordingly high, 275° d. for glycine anhydride. The N,N′-dimethyl derivative, as expected for compounds in which hydrogen bonding is eliminated, melts lower—at 149 to 150°—and boils with only slight decomposition at about 350°.

Examination of the crystal structure[97] by X-rays shows that the diketopiperazine molecule is nearly a plane hexagon. The C—O and C—N bond distances are 1.25 and 1.33 A., respectively, which values agree with those in other resonating systems such as in urea or thiourea. The CH_2—N and CH_2—C distances are less than the usual single-bond values of 1.47 and 1.54 A., though the CH_2—N value (1.41 A.) is nearly the same as in hexamethylene tetramine. In general, infrared absorption studies[98] agree with these results. No —OH linkages appear to be present.

---

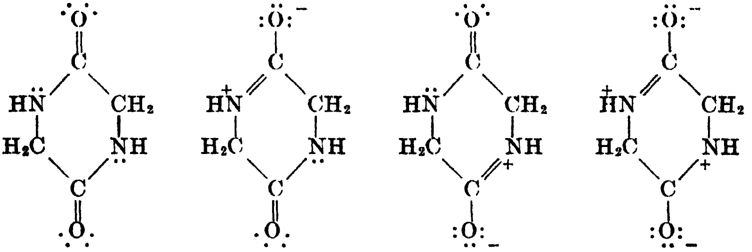
[95] Forsee and Pollard, *J. Am. Chem. Soc.*, **57**, 2363 (1935).

[96] Fourneau and Barrelet, *Bull. soc. chim.* [4], **45**, 1172 (1929).

[97] Corey, *J. Am. Chem. Soc.*, **60**, 1598 (1938).

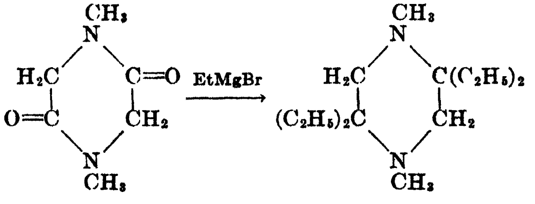
[98] Kellner, *Proc. Roy. Soc.* (*London*) *A*, **177**, 447 (1941).

Resonance occurs between the C—N and C—O bonds. The probable forms are shown below.



Titration curves[99] for diketopiperazine show that there is no acid binding and only a slight alkali binding. Extended alkali or acid treatment will, of course, ultimately give amino acids. If the dry sodium salt of the anhydride, prepared by evaporation of methanol from the sodium alkoxide solution, is treated with benzyl chloride, the N,N-dibenzyl derivative is obtained.[100] The position of the benzyl substituents on the nitrogen instead of the oxygen atoms is decided by the fact of their elimination by dilute mineral acid, a circumstance unlikely for an oxygen ether. The N-hydrogen atom can also be replaced by a sulfonyl group when treated with N-pyridonium sulfonic acid, an exceedingly mild reagent.[101] Practically all evidences of the presence of active hydrogen atoms are, therefore, limited to activity on the nitrogen atom.

Since these compounds tend to be somewhat like amides, the methylene group is not especially active, although condensation will occur when the diketopiperazine is heated with a reactive aldehyde, acetic anhydride, and sodium acetate.[102] Similarly, the keto group lacks the reactions of a ketone, since no phenylhydrazine is formed. Nevertheless the Grignard reagent,[103] ethylmagnesium bromide, reacts with sarcosine anhydride in anisole solution to form 2,5-tetraethyl-N,N′-dimethylpiperazine. By a similar reaction with phenylmagnesium bromide, however,



---

[99] Stiasny and Scotti, *Ber.*, **63**, 2977 (1930); Konikov and Nazarov, *Arch. sci. biol. U.S.S.R.*, **39**, 505 (1935); *C.A.*, **30**, 6023 (1936).

[100] Gränacher, Wolf, and Weidinger, *Helv. Chim. Acta*, **11**, 1228 (1928).

[101] Baumgarten, Marggraff, and Dammann, *Z. physiol. Chem.*, **209**, 145 (1932).

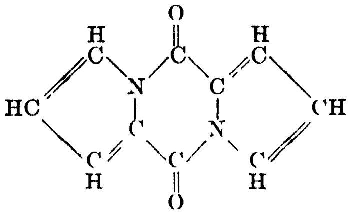
[102] Ueda, *J. Chem. Soc. Japan*, **50**, 502 (1929); *Ber.*, **61**, 146 (1928).

[103] Kapfhammer and Matthes, *Z. physiol. Chem.*, **223**, 43 (1933).

the ring is cleaved and methylaminoacetophenone, $CH_3NHCH_2C(O)C_6H_5$, and sarcosylmethylacetophenone, $CH_3NHCH_2C(O)N(CH_3)CH_2C(O)C_6H_5$, are formed.

These diketopiperazines are important because they are present among the products of protein hydrolysis[104] and are, therefore, one of the components of proteins. Silk fibroin, for instance, yields glycylalanine anhydride, glycyltyrosine anhydride, and alanylserine anhydride when treated with concentrated hydrochloric acid or 70 per cent sulfuric anhydride.

Sarcosine anhydride can be synthesized from methyl amine sulfate, 40 per cent formalin, and potassium cyanide, followed by treatment of the sarcosine nitrile with absolute alcohol and hydrogen chloride.[105] Pyrocoll

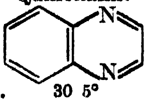


is the tricyclic anhydride prepared by treatment of pyrrole-α-carboxylic acid with acetic anhydride.

Quinoxalines are obtained by condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds. The reaction is used frequently as a test for the presence of adjacent carbonyl groups.

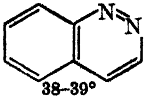
In contrast to the case of pyrazine and its isomers, the melting point of quinoxaline is lower than that of any of its isomers. This circumstance can be compared with quinoline (m.p. −22.6) and isoquinoline (m.p 25°) in which it is clear that the melting point is lower when a nitrogen atom is adjacent to the ring than when one carbon atom removed. Since quinoxaline has two nitrogen atoms adjacent to the ring, it has the lowest melting point; since phthalazine has both nitrogen atoms one carbon atom removed from the ring, it has the highest melting point. These two benzodiazines melt 65 and 53°, respectively, higher than the corresponding monazine or a little less than the 74° increment noted on page 391

Quinoxaline



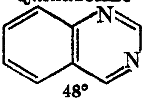
M.p. 30 5°
B.p. 226

Cinnoline



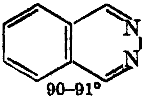
38–39°

Quinazoline



48°
243

Phthalazine



90–91°
315

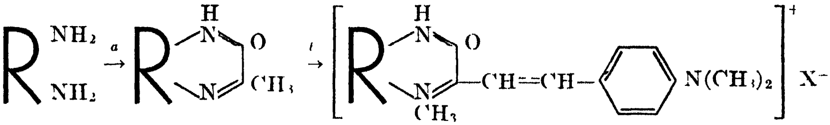
---

[104] ABDERHALDEN and STIX, *Z. physiol. Chem.*, **132**, 238 (1924); ABDERHALDEN, *ibid.*, **265**, 23 (1940).

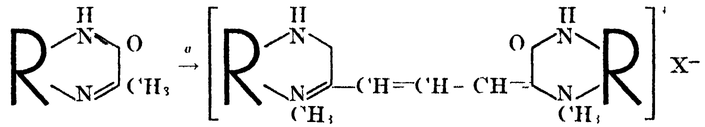
[105] STAUDT, *Z. physiol. Chem.*, **146**, 286 (1925).

for the benz group. Cinnoline and quinazoline, each with one nitrogen atom adjacent to and one remote from the benzene ring, have melting points between the two extremes; and the value of the latter is somewhat higher than that of the former in accordance with the previous observation that pyrimidine melts higher than pyridazine.

Quinoxaline cyanines that have an oxygenated ring are prepared by conventional reactions with the methiodide salt of the product of condensation of *o*-phenylenediamine and pyruvic acid.[106] Two examples are shown below.

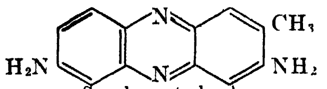


[a] Condensation with $CH_3C(O)CO_2H$. [b] $(CH_3)_2SO_4$, $OHC{\cdot}C_6H_4N(CH_3)_2$

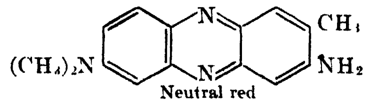


[a] Formamidine.

A number of important *phenazines* are related to the dyes. Simple neutral red and neutral red—the latter called toluylenroth by Witt,[107] the discoverer of this series of dyes—are good histological and vital stains, acid-base indicators such as in neutral red paper, and oxidation-reduction indicators.[108] The formula of these compounds, shown respectively below, is similar to that of methylene blue and other compounds already described. These compounds are prepared by oxidation of a mixture of 2,4-diaminotoluene with *p*-phenylenediamine or *p*-aminodimethylaniline by potassium dichromate. The first product is an indamine, known as toluene blue that occurs in the preparation of neutral red. Boiling water converts the indamine to neutral red and a dihydro product, and the latter in turn is oxidized by more of the reagent to neutral red. One of the resonance forms of the dye is shown below.



Simple neutral red



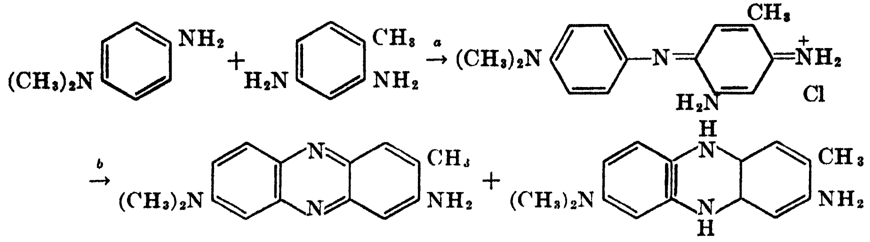
Neutral red

---

[106] Cook and Perry, *J. Chem. Soc.*, 394 (1943); Cook and Naylor, *ibid.*, 710 (1942).

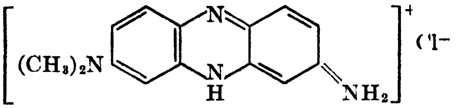
[107] Witt, *Ber.*, **12**, 931 (1879).

[108] Clarke and Perkins, *J. Am. Chem. Soc.*, **54**, 1228 (1932).



[a] $K_2Cr_2O_7$. [b] Boiling water.

Dyes of this class are known as eurhodines.



The phenazine structure of these dyes is shown by elimination of the amino groups from simple neutral red and comparison of the 2-methylphenazine so produced with that prepared from pyrocatechol and *o*-toluylenediamine.[109]

Mauve, sometimes called mauveine or Perkin's violet, is a safranine type dye, made famous as the first synthetic dyestuff.[110] It was in 1856 that the eighteen-year-old Perkin attempted the synthesis of quinine by bichromate oxidation of the salt of an alkyltoluidine. By present-day standards, such an idea seems preposterous, but according to the theory of that period, a natural product could be synthesized if the elements composing it were brought together in the right proportions. As far back as 1849, the synthesis of quinine by hydration of naphthylamine had been predicted; and to Perkin, the formation of quinine from an alkyltoluidine according to the equation below was eminently sound.

$$2C_{10}H_{13}N + 3O \rightarrow C_{20}H_{24}N_2O_2 + H_2O$$

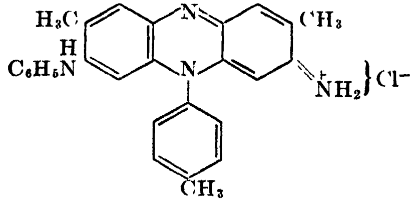
The dirty red-brown precipitate first obtained led him to repeat the experiment with the salt of a simple base, aniline, which happened to contain some toluidines. The dye thus accidentally formed in small yield induced Perkin to undertake its commercial production. By 1859, the value of the dye was apparent, particularly to the French printers who gave it the name of "mauve." Meanwhile, Perkin improved the methods for the production of the necessary nitrobenzene and aniline; but this greater availability of aniline stimulated interest in its properties and soon led to the discovery of the more brilliant, though less stable, magenta and its derivatives which competed successfully with Perkin's violet. Actually, the production of mauve flourished only about 10 years. Perkin, meanwhile, maintained his interest in chemical research and in 1867 discovered the coumarin synthesis and shortly thereafter the cinnamic acid synthesis. He severed his connection in 1874 with the company that he founded and devoted the remainder of his life to research work. While his discovery was a primary factor in the founding of the great coal-tar dye and related industries, his country, where the dye industry began, did not acquire leadership in the field. Hofmann, the professor under whom Perkin studied, left London in 1865. Not until 1874 was there another professorship in organic chemistry in England, a circumstance that obviously led to a lack of trained men at a time when such men could ill be spared. Subsequently, the coal-tar industry was to become a problem of great concern for national welfare and defense.[111]

---

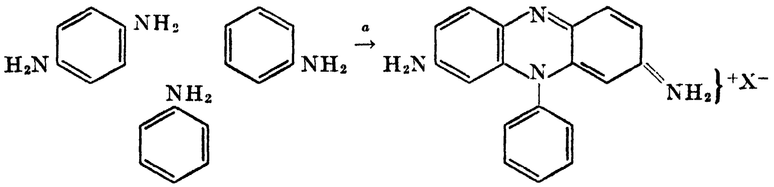
[109] BERNTHSEN and SCHWEITZER, *Ann.*, **236**, 332 (1886).

[110] MELDOLA, *J. Chem. Soc.*, **93**, 2214 (1908).

The formula for mauve is shown below.



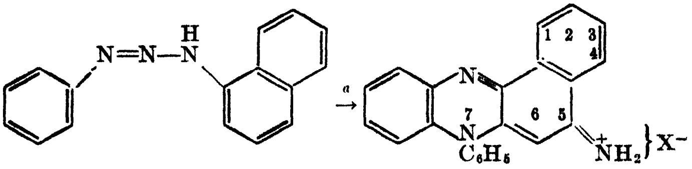
The parent *safranine dye* is made by oxidation of a mixture of *p*-phenylenediamine and aniline.



^{a} Oxidation, HX.

Nitrous acid, followed by boiling ethanol eliminates one amino group and forms *aposafranine.* The second amino group is similarly eliminated after diazonium formation in concentrated sulfuric acid.

Rosinduline dyes are made by the fusion of an aminoazo compound with a primary aromatic base.[112]



^{a} The hydrochloride, heated with two parts of aniline at 160 to 170°.

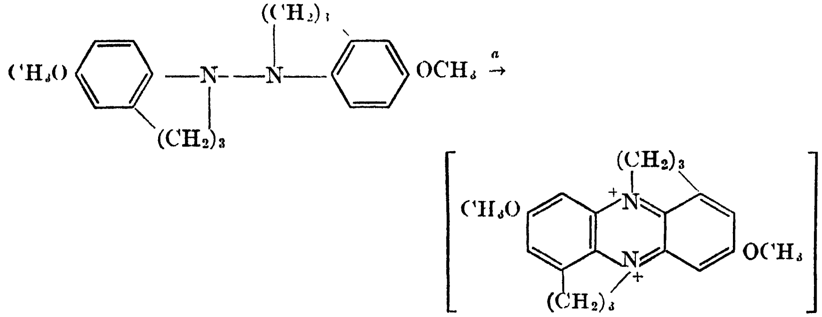
---

[111] GARVAN, *Ind. Eng. Chem.*, **13**, 867 (1921); U.S. Tariff Commission Report, 1936; editorials in *Ind. Eng. Chem.*, **9**, 1084 (1917); **10**, 792 (1918); **13**, 502 (1921).

[112] FISCHER and HEPP, *Ann.*, **256**, 233 (1890); **262**, 237 (1891).

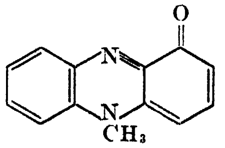
The structure of rosinduline (m.p. of free base is 199°) is shown by hydrolysis at C_5 to rosindone (m.p. 259°) with concentrated hydrochloric acid at 160 to 180°, followed by conversion to the known α-naphthaphenazine (m.p. 142°) by zinc-dust distillation. Phenylrosinduline is prepared from the same components by fusion at 140 to 150°; and the structure is the same as that of rosinduline except for the $=NC_6H_5$ instead of the $=NH$ at C_5.

Thalloperazine is a phenazine formed by an *o*-semidine rearrangement.[113] 6-Methoxytetrahydroquinoline is converted to a hydrazine derivative by mild permanganate oxidation, and the phenazine is then formed by the action of hydrochloric acid on the bistetrahydroquinolyl compound. Scarlet-red needles of the meriquinoid azonium chloride, formed by autoxidation, deposit from the solution.



a HCl.

Pyocyanine is the blue coloring matter of *Bacillus pyocyaneus*, frequently found in purulent wounds. Alkali, in the presence of air, hydrolyzes it to 1-hydroxyphenazine; catalytic reduction gives 5-methyl-1-hydroxydihydrophenazine, which is reoxidized by air to pyocyanine. These facts and the synthesis[114] from α-hydroxyphenazine methosulfate and alkali are in accordance with the ortho quinoid structure below. The molecular weight in glacial acetic acid is twice the value expected, but this result is probably caused by association, since the oxidation-reduction potentials[115] indicate that the formula is monomolecular.



---

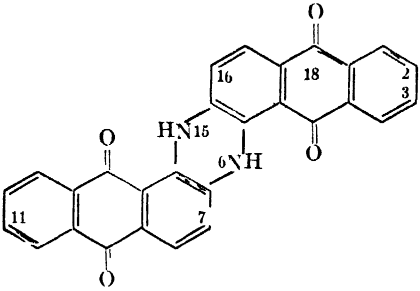
[113] WIELAND and HAAS, *Ber.*, **53**, 1336 (1920).

[114] WREDE and STRACK, *Z. physiol. Chem.*, **181**, 58 (1929); *Ber.*, **62**, 2051 (1929).

[115] MICHAELIS, *Chem. Rev.*, **16**, 273 (1935); MICHAELIS and SCHUBERT, *ibid.*, **22**,

Below pH 6, reversible reduction of pyocyanine occurs in two stages. Each ion is capable of adding a proton. The reaction is typical of all quinones. The product of the first reduction stage is called a "semiquinone," that of the complete reduction is called a "meriquinone." The separate stages are detected by a graph of the potential against the per cent reduction as well as by a color change. The semiquinone is a free radical, stabilized by resonance.

Indanthrone, known as indanthrone blue R, is a vat dye obtained by fusion of 2-aminoanthraquinone with potassium hydroxide at 200 to 250°, followed by aerial oxidation of the potassium salt of the hydrocompound.[116] The compound crystallizes as a blue copperlike product from boiling quinoline, and is extremely stable. It can be heated in air at 470°, with concentrated hydrochloric acid at 400°, and with potassium hydroxide at 300° without being decomposed. Phosphorus and hydriodic acid at 210 to 220° or zinc-dust distillation convert it to anthrazine.



Flavins.—A large number of water-soluble nitrogenous fluorescent dyes exist in nature. They are present in bacteria, yeast, wines, the glowworm, eyes of certain fish, whey, and numerous other places. They are named according to their source, behavior, or the material with which they are combined. Hence the expressions lactoflavin, oroflavin, photoflavin, lumiflavin, riboflavin, flavoprotein, etc.

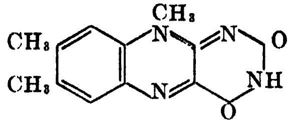
Lactoflavin, $C_{17}H_{20}N_4O_6$, the yellow coloring matter isolated[117] from the whey of fresh milk (1 g. from 5,400 l.), is illuminated in alkali solution in order to detach the side chain and form lumilactoflavin, $C_{13}H_{12}N_4O_2$, which loses urea when boiled with alkali. Subsequent pyrolytic elimination of a carboxyl group gives $C_{11}H_{12}N_2O$. These results can be satisfactorily explained on the basis that lumiflavin is an N-methylisoalloxazine.

---

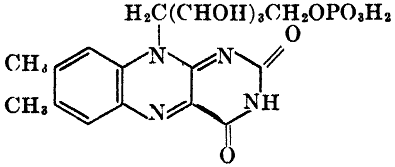
437 (1938); Michaelis, Schubert, Reber, Kuck, and Granich, *J. Am. Chem. Soc.*, **60**, 1678 (1938); see also Elema, *Rec. trav. chim.*, **50**, 907 (1931).

[116] Scholl, *Ber.*, **36**, 3410 (1903); Scholl and Berblinger, *ibid.*, **36**, 3427 (1903).

[117] Kuhn, *et. al.*, *ibid.*, **66**, 1950 (1937).

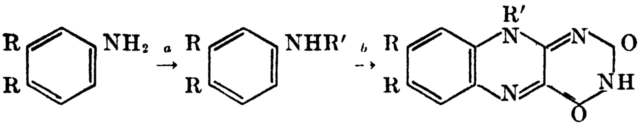


In nature, the compound is combined with *d*-ribose, and is therefore sometimes called a riboflavin.[118] A phosphoric acid radical is attached to the sugar.



Chemically, the compound is a phosphoric acid ester of 7,8-dimethyl-10-*d*,1′-ribitylisoalloxazine; in common language it is vitamin B_2, the growth-promoting factor, without which animals fail to grow, lose their hair, have dermatitis, and exhibit premature aging.[63]

Compounds of the flavin type can be synthesized[119] by condensation of *o*-phenylenediamine derivatives with alloxan, as illustrated below.

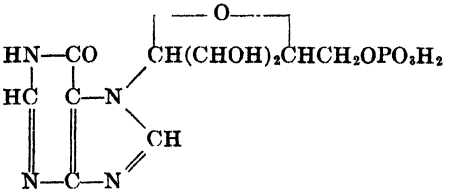


R = alkyl group. R′ = sugar group.
[a] d-Ribose, H_2 + Ni. [b] $C_6H_5N_2Cl$, $Na_2S_2O_4$, alloxan.

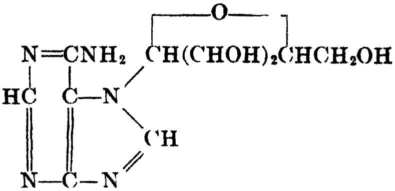
The occurrence of such nitrogen-containing compounds attached to sugars has occasioned some speculation on the process by which the nitrogen in nitrates is converted by the plant to organic compounds.[120] Although the manner of this change is obscure, nitrogen frequently appears to be attached to the C_2 of a sugar, while the C_1 is converted to a carboxyl group. The various amino acids such as tryptophan and histidine are examples of such a possible change; and the occurrence of sugar in lactoflavin, inosic acid, and adenosin can be regarded as furnishing vestigial evidence of this point.

---

[118] Kuhn, Rudy, and Weygand, *ibid.*, **69**, 1543 (1936).
[119] Karrer and Guibett, *Helv. Chim. Acta*, **19**, 1034 (1936).
[120] Hall, *Chem. Rev.*, **20**, 305 (1937).



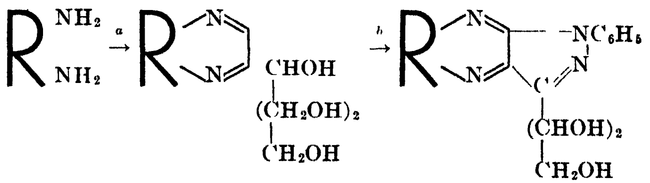
Inosic acid



Adenosin

In both of these examples, as in lactoflavin, the sugar is attached to an —N—C=N— system.

Flavazoles are condensed quinoxaline-pyrazole systems. Some compounds in this series can be prepared by the action of glucose with *o*-phenylenediamine, followed by treatment of the quinoxaline product with phenylhydrazine.[121]

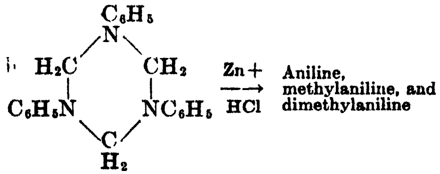


[a] Glucose. [b] $C_6H_5NHNH_2$.

TRIAZINES AND RELATED COMPOUNDS

A considerable number of symmetrical molecules with three like hetero atoms in the ring are derived by polymerization of comparatively simple compounds such as Schiff bases, cyanic acid, nitriles, and formaldehyde. In many of these cases, the ring is readily broken by heat and the monomer recovered. The resonance that stabilizes pyridine and other rings is of a very low order or absent in these cases. The evidence that such compounds exist in a ring form sometimes rests only on the fact that the compound is trimeric or that the unit survives some simple chemical change.

Schiff bases of simple type $RCH{=}NR'$ are polymerized if the molecular weight is low, particularly if they are derived from formaldehyde. Methyleneaniline, for example, is trimeric in benzene, nitrobenzene, ethylene bromide, and 1,4-dioxane, but is more nearly dimeric in molten camphor. When reduced by zinc dust and concentrated hydrochloric acid, the products are N-methyl substituted anilines, whose presence

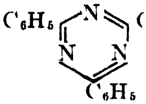


---

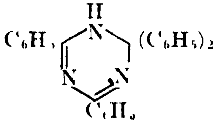
[121] OHLE and MELKONIAN, *Ber.*, **74**, 279 (1941).

accords with the view that a methylene group is attached to nitrogen in the original compound.[122] Methylene-*p*-toluidine shows, in general, the same behavior. Acetaldehyde and aniline, however, in the cold form the ethylidene dianiline, $(C_6H_5NH)_2CHCH_3$, which changes to a dimer when warmed.

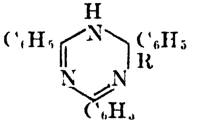
Cyaphenine is made from benzonitrile by the polymerizing action of chlorosulfonic acid (40 per cent yield),[123] concentrated sulfuric acid,[124] or sodium.[125] The action of sodium on benzonitrile in hot benzene leads also to 2,2,4,6-tetraphenyl-1,2-dihydro-1,3,5-triazine[126] and sodium cyanide. Dihydrotriazines are obtained also from benzonitrile and ethyllithium and other like organolithium reagents and from isopropyl- or phenyl-magnesium bromide, one of the phenyl groups being replaced by R in the above formula, where R = methyl, ethyl, butyl, isopropyl, or phenyl. The dihydro compounds, as expected, are strong bases. They yield mono-*p*-toluenesulfonylchloride derivatives, which are insoluble in caustic alkali and form N-nitroso derivatives in accordance with the properties of secondary amines. They are comparatively stable to permanganate, chromic acid, and aqueous caustic potash. Thirty per cent sulfuric acid slowly attacks them and forms ketones. At 250 to 300°, the methyl-, ethyl-, *n*-propyl-, and *n*-butyl- (but not isopropyl) dihydro compounds lose ammonia and form triphenylpyrimidines.

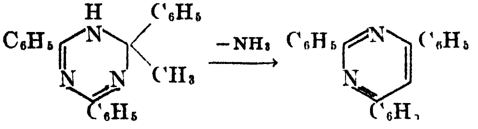


Cyaphenine



2,2,4,6-Tetraphenyl-1,2-dihydro-1,3,5-triazine





Attempted reduction of cyaphenine in acid solution gives lophine by loss of one ammonia. Nitration of cyaphenine gives an impure product, but nitrocyaphenines can be prepared[123] by heating ammonium chloride and aluminum chloride with mixtures of benzonitriles and benzoyl chloride, one component of which is nitrated. For example, benzonitrile and *m*- or *p*-nitrobenzoyl chloride so treated give *m*- or *p*-nitrocyaphenine.

---

[122] WAGNER, *J. Am. Chem. Soc.*, **54**, 660 (1932); MILLER and WAGNER, *ibid.*, **54**, 3698 (1932).

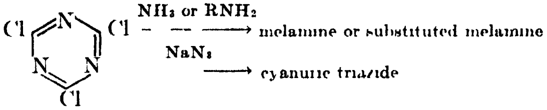
[123] COOK and JONES, *J. Chem. Soc.*, 278 (1941).

[124] PINNER and KLEIN, *Ber.*, **11**, 764 (1878).

[125] HOFMANN, *ibid.*, **1**, 198 (1868).

[126] ANKER and COOK, *J. Chem. Soc.*, **323** (1941).

Cyanogen chloride, a liquid prepared from hydrocyanic acid and chlorine, polymerizes readily in the presence of a little free halogen to cyanuric chloride (m.p. 145°, b.p. 190°). The ring structure is evident from the fact that it is preserved through a number of transformations.



Furthermore, the halogen atoms in cyanogen chloride can be replaced one at a time by successive treatments with ammonia, methylamine, and ethylamine, and the same substituted melamine obtained irrespective of the order of replacement.[127]

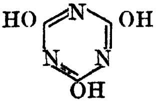
Melamine, or 2,4,6-triamino-s-triazine, was first prepared by Liebig in 1834 from ammonium chloride and potassium thiocyanate but is now commonly obtained from cyanamide or dicyanamide, which in turn are obtained from calcium cyanamide. It is a weak base, crystallizes readily

$$CaCN_2 \xrightarrow{HX} H_2NCN \rightarrow H_2NC(=NH)NH—C\equiv N \xrightarrow{\text{heat}} \text{melamine}$$

from water, and sublimes if heated carefully. The compound is of considerable commercial interest because it forms synthetic resins with formaldehyde. Resinification probably occurs through the formation of $HOCH_2NCH_2OH$ systems as intermediates. The melamine resins are similar and sometimes superior to the urea resins.[128]

Cyanuric triazide is obtained from cyanuric chloride and sodium azide. It melts at 94° and explodes above 170°. The compound has some interest as a detonating agent, such as silver or lead azide.[129] Catalytic reduction over palladium converts it to melamine.[130]

Cyanic acid polymerizes readily to *cyanuric acid*, a compound slightly soluble in water and less soluble in ether. In contrast to barbituric acid, the compound has only a weak acidity. The molecule is easily broken apart by heat to cyanic acid.



Hexamethylene tetramine results when ammonia is added to formaldehyde, and the mixture is evaporated. The compound[131] is one of the few known organic products without salt character which has cubic symmetry. X-ray data show that the structure is that of a condensed *s*-triazine system. Four ring systems can be counted. Strong acids

---

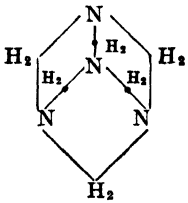
[127] Diels, *Ber.*, **32**, 692 (1899).

[128] Hodgins, Hovey, Hewett, Barrett, and Mieske, *Ind. Eng. Chem.*, **33**, 769 (1941).

[129] Ott and Ohse, *Ber.*, **54**, 179 (1921).

[130] Wienhaus and Ziehl, *ibid.*, **65**, 1461 (1932).

[131] Dickenson and Raymond, *J. Am. Chem. Soc.*, **45**, 22 (1923).



decompose the compound readily. Phenols, heated with hexamethylene tetramine in the presence of glyceroboric acid at 160°, and then steam distilled in the presence of sulfuric acid give an *o*-hydroxyaldehyde. The method is faster and sometimes better in yield than the Reimer-Tieman process.[132] The possible steps are shown in the equation below in which R is C_6H_4.

$$3HORH + C_6H_{12}N_4 \rightarrow NH_3 + 3HORCH_2N{=}CH_2$$
$$HORCH_2N{=}CH_2 \rightarrow HORCH{=}NCH_3$$
$$HORCH{=}NCH_3 + H_2O \rightarrow RCHO + CH_3NH_2$$

The method is in part similar to that of Sommelet's[133] in which benzyl chloride is converted to benzaldehyde when heated with hexamethylene tetramine in aqueous alkali. Sommelet assumed that the intermediate step, $C_6H_5CH_2N{=}CH_2 \rightarrow C_6H_5CH{=}NCH_3$, occurred.

Thiophenol gives a triamine[134] when refluxed with the tetramine in dioxane solution.

$$6C_6H_5SH + (CH_2)_6N_4 \rightarrow 2N(CH_2SC_6H_5)_3 + 2NH_3$$

Nitration of the tetramine with 96 per cent nitric acid at 0° gives 1,3,5-trinitrohexahydro-s-triazine, called hexogen,[135] which is a powerful explosive. Nitrous acid gives dinitrosopentamethylenetetramine.

Hexamethylene tetramine has been used some as a urinary antiseptic under the name of "urotropine." Its action depends on the slow liberation of formaldehyde in the slightly acid medium.

Cyameluric acid is a condensed triazine system[136] that bears the same relation to the simple triazine system as do the condensed benzene rings to benzene. It is prepared by alkali treatment of a hydromelonate,

---

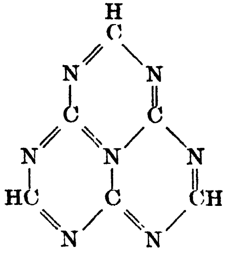
[132] Duff, *J. Chem. Soc.*, **547** (1941).

[133] Sommelet, *Compt. rend.*, **157**, 852, 1443 (1913).

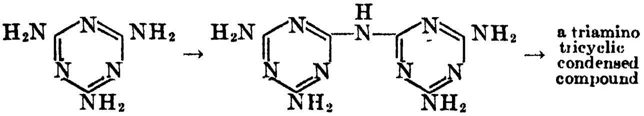
[134] Dougherty and Taylor, *J. Am. Chem. Soc.*, **55**, 4588 (1933).

[135] Desvergnes, *Chimie & industrie*, **28**, 1038 (1932); Stettbacher, *Nitrocellulose*, **11**, 63 (1940); *C.A.*, **35**, 4953 (1941).

[136] Pauling and Sturdivant, *Proc. Nat. Acad. Sci.*, **23**, 615 (1937).



$C_9H_3N_{13}$, itself produced by heating potassium ferricyanide with sulfur or fusing potassium thiocyanate with antimony trichloride. The triamino derivative can be obtained from melamine by a two-step loss of ammonia.[137] This compound is called "melem."



$C_3H_6N_6$ → $C_6H_9N_{11}$ → $C_6H_6N_{10}$

Melamine Melam Melem

A considerable number of other symmetrical heterocyclic systems exist, which do not have nitrogen in the ring. They are formed, like the triazines, as the products of polymerization. Among these are the well-known trioxymethylene, paraformaldehyde, trithiane, the trithiane-trisulfoxides, known often as trimethylenetrisulfoxide, and the corresponding sulfone. Trithiane[138a] is the product of polymerization of thioformaldehyde, prepared from sodium thiosulfate, formaldehyde, and hydrochloric acid, as shown below.

$$HO_3SSSO_3H + H_2CO \rightarrow HO_3SSSO_3CH_2OH$$
$$3HO_3SSSO_3CH_2OH + 3H_2O \rightarrow (CH_2S)_3 + 6H_2SO_4$$

The two oxygenated trithianes are derived by peroxide and permanganate oxidation, respectively. The former is soluble in aqueous alkali, the latter in aqueous carbonate solution.

TETRAZINES

Diazoacetic acid undergoes dimerization with strong alkali or ammonia to a dihydro product, which by oxidation gives the 3,6-dicarboxylic acid of 1,2,4,5-tetrazine, the alkali solution of which is deep red in color. Careful decarboxylation—the process can occur explosively—gives tetrazine, a purple-red compound that melts at 99°, has a purple-red vapor, and decomposes in light.[138b] The diphenyl derivative,[139] prepared from benziminoether by reaction with hydrazine, is more stable. Its red crystals melt at 192°.

---

[137] McClellan, *Ind. Eng. Chem.*, **32**, 1181 (1940); Redemann and Lucas, *J. Am. Chem. Soc.*, **62**, 842 (1940).

[138] (*a*) Vanino and Schinner, *Ber.*, **47**, 1776 (1914); (*b*) Curtius and Rimele, *ibid.*, **41**, 3116 (1908).

When a saturated aqueous solution of urea is treated with chlorine, crystals of dichlorocarbamide, ClNHC(O)NHCl, separate in spite of the ease of hydrolysis of the chloride. Strong aqueous ammonia converts this compound to *p*-urazine,[140] a diketotetrazine, $OC(NHNH)_2CO$. This compound is stable to concentrated sulfuric acid on a water bath but not at 120 to 130°.

Problems

1. What is the formula of the product produced in the following reactions? (*a*) Barbituric acid and isatin-α-anilide in the presence of acetic anhydride.[141] (*b*) Isatin and *o*-phenylenediamine.[142] (*c*) *p*-Tolunitrile, added slowly to chlorsulfonic acid at 0° and the mixture allowed to stand overnight.[123] (*d*) Acetamidine and malonitrile in alcoholic sodium ethoxide to give $C_7H_8N_4$.[143] (*e*) Two molecules of formamidine and one of malononitrile in alcoholic sodium ethoxide to give $C_5H_5N_4$.[144] (*f*) Acetamidine condensed with benzamidine.[145] (*g*) Thiocarbanilide treated with methyl sulfate and the product allowed to react with an N-substituted α-amino acid.[146]

2. What is the product formed in each of the following sequence of reactions? (*a*) Benzeneazomalononitrile, $C_6H_5N{=}N{-}CH(CN)_2$ (how prepared?), treated with formamidine in alcoholic sodium ethoxide, and the product reduced with hydrogen over Raney nickel at 100°/60 atm. to give $C_4H_7N_5$. This last compound in turn is treated with sodium dithioformate in cold water and the product then refluxed in water while hydrogen sulfide is evolved. The final compound, $C_5H_5N_5$, is obtained in 50 per cent over-all yield, calculated on the malonitrile, and is a good preparative method.[144] (*b*) 2-Methyl-5-cyano-6-aminopyrinidine (how prepared?) treated with aqueous potassium hydroxide, and the product therefrom allowed to react with methyl alcohol in concentrated sulfuric acid. The $C_7H_9N_3O_2$ product is then treated successively with (1) hydrazine, (2) benzenesulfonyl chloride, and (3) sodium carbonate to give $C_6H_7N_3O$.[147]

3. *m*-Tolyl- and *p*-tolyl phenyl ether are each heated with 1 mole of sulfur and 0.5 mole of anhydrous aluminum chloride. What product is formed in each case, and which ether would probably give the higher yield of product?[148]

4. The *o*-nitrobenzylamide of y-phenyoxybutyric acid, $NO_2C_6H_4CH_2NHC(O)(CH_2)_3OC_6H_5$ (how prepared?), is in turn (1) subjected to catalytic hydrogenation over platinum oxide, (2) heated at 270°, (3) treated with hydrogen bromide, and (4) treated with alkali to give $C_{11}H_{14}N_2$.[85] What is the final compound?

---

[139] Bamberger, *ibid.*, **33**, 3197 (1900); Darapsky, *J. prakt. Chem.* [2], **97**, 184 (1918).

[140] Chattaway, *J. Chem. Soc.*, **95**, 235 (1909).

[141] Felix and Friedländer, *Sitz. Ber.*, 118 [11B], 750 (1909).

[142] Marchlewski, *Ber.*, **28**, 2528 (1895).

[143] Baddiley, Lythgoe, Todd, and Tophan, *J. Chem. Soc.*, 388 (1943).

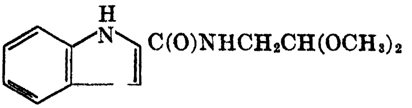
[144] Baddiley, Lythgoe, and Todd, *ibid.*, 386 (1943).

[145] Dox and Yoder, *J. Am. Chem. Soc.*, **44**, 361 (1922).

[146] Deck and Dains, *ibid.*, **55**, 4986 (1933).

[147] Price, May, and Pickel, *ibid.*, **62**, 2818 (1940).

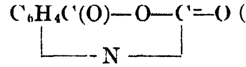
[148] Suter and Green, *ibid.*, **59**, 2578 (1937).



5. When the indole derivative shown at the side is treated with alcoholic hydrochloric acid, ring closure occurs. The product may be either a diazine or a carboline, depending on the position of ring closure. What tests might be applied to differentiate between the possibilities?[149]

6. When 3-aminopyridine-4-carboxylic acid (how prepared?) is treated with urea at 170° for 3 hr., a $C_7H_5N_3O_2$ product is obtained which does not melt but sublimes at 430°, is easily soluble in warm dilute hydrochloric acid and in alkali. What compound is formed? What would be the product had formamide been used in place of urea?[150]

7. When the amide of 2-methyl-5-cyanopyridine-4-carboxylic acid (show a method for the preparation of this starting material by a series of steps from cyanoacetamide as one component[151]), is treated with sodium hypochloride in alkaline solution, two compounds, $C_8H_7N_3O_2$ and $C_6H_9N_3$, are formed in the proportion of 9 parts to 1. What are the reactions that probably occur?[152]

8. Isatoic anhydride,  $\underbrace{C_6H_4C(O)—O—C{=}O}_{N}$ (how prepared?), serves as an active agent for the introduction of an anthranoyl group. What is the product of the reaction of this anhydride with a diarylamidine ArN=CH—NHR (how prepared?)?[153]

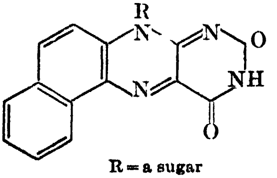
9. When 2,3,5,6-tetrachloronitrobenzene is heated with alcoholic ammonia at 200°, 2,3,5,6-tetrachloroaniline is formed as one product together with another which by reduction with aqueous-alcoholic sodium hydrosulfite and subsequent treatment with 9,10-phenanthraquinone gives a $C_{20}H_9N_2Cl_3$ compound. What is the nature of this second product?[154]

10. 6-Nitro-3-acetaminobenzoic acid (how prepared?) yields an anthranil when treated with acetic anhydride; and the anthranil, when shaken with an excess of dilute ammonia, gives a $C_9H_7N_3O_3$ product (m.p. 277 to 278°) which dissolves in dilute alkali and forms a crystallin nitrate in nitric acid. What is the reaction that occurs?[155]

11. Suggest a method for the synthesis of (*a*) 3,7-dimethyluric acid,[156] (*b*) theobromine,[157] (*c*) theophylline.[157]

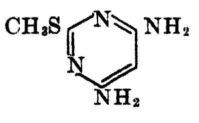
12. Devise a method for the preparation of each of the following compounds:

A[119]



R = a sugar

B[144]



---

[149] KERMACK, PERKIN, and ROBINSON, *J. Chem. Soc.*, **119**, 1627 (1921).

[150] GABRIEL and COLMAN, *Ber.*, **35**, 2831 (1902).

[151] BARDHAM, *J. Chem. Soc.*, 2223 (1929).

[152] REIDER and ELDERFIELD, *J. Org. Chem.*, **7**, 286 (1942).

[153] MEYER and WAGNER, *ibid.*, **8**, 239 (1943).

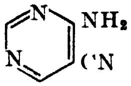
[154] PETERS, ROWE, and STEAD, *J. Chem. Soc.*, 576 (1943).

[155] BOGERT and CHAMBERS, *J. Am. Chem. Soc.*, **27**, 649 (1905).

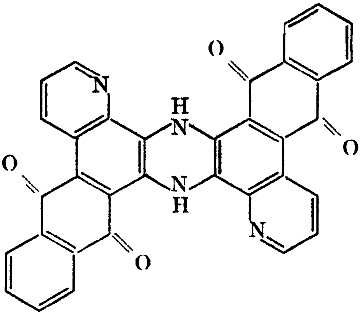
[156] FISCHER, *Ber.*, **30**, 559, 1839 (1897).

[157] TRAUBE, *ibid.*, **33**, 3047, 3052 (1900).

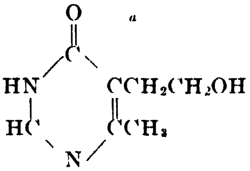
C[158]



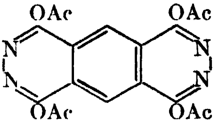
D[159]



E[160] [a]



F[161]



[a] The intermediate for the preparation of the pyrimidine analogue of thiamin bromide.

[158] Baddiley, Lythgoe, and Todd, *J. Chem. Soc.*, 571 (1943).

[159] Scheidt, *J. prakt. Chem.*, **157**, 203 (1941).

[160] Tola and Elderfield, *J. Org. Chem.*, **7**, 309 (1942).

[161] Seka, Sedlatschek, and Preissecker, *Monatsh.*, **57**, 86 (1931).

INDEX

A

Abbreviations (*see* list in Chemical Abstracts)
Acetoacetates, preparation of 1,4-diketones from, 3
Acetomorphine, 318
Acetylene, reaction of, with diazomethane, 369
  with hydrazoic acid, 369
  with sulfur, 40
Acetylene dicarboxylate, addition of, to diazomethane, 369
  to furan, 7
  to pyridine, 196, 236
  to pyrroles, 66
  to quinoline, 298_{2b}
Acid chlorides, catalytic reduction of, 458
  reaction of, with diazomethane, 369
Acidity, of allantoin, 461
  of alloxan, 488
  of azoles, 405
  of azolones, 488, 489
  of barbituric acid, 487
  of hydroxyuracil, 488
  of imidazoles, 405
  of malonic esters, 488
  of 1-phenyl-5-mercaptotetrazole, 380
  of phloroglucinol, 488
  of pyrroles, 60
  of rhodanine, 430
  of tetrazoles, 405
  of triazoles, 405
Acids, α-amino, alkaloids from, 312
  oxazoles from, 380
  preparation of, from azlactones, 128, 421
    from hydantoins, 459
    from piperidines, 241
    from rhodanine, 431
  synthesis of, 453
 α,γ-amino, from decomposition of hydantoinpropionate, 452
Acids, β-amino, 454
  unsaturated, esters of, 235
 α-hydroxy, conversion of, to aldehyde, 153
   to ketones, 451
 α-keto, preparation of, from azlactones, 175
   from rhodanines, 431
  pyrroles from, 59
 γ-keto, preparation of, from furfuryl alcohols, 8
 α-mercapto, preparation of, from rhodanines, 431
 tertiary carboxylic, preparation of, from furan, 12
 α-thiohydroxy, preparation of, from rhodanines, 431
Acridine, 332
 9-chloro, 333
 9-dibromo, 333
 9-dimethyl, 340
Acridine compounds, naming and numbering of, 326
 preparation of, 329, 334
 therapeutic activity of, 339
Acridine orange, 336–338
Acridine yellow, 336, 338
Acridine-9-carboxylic acid, 332, 335
Acridines, 326
 amino, bacteriostatic index of, 339
Acridinic acid, 285
Acridinium salts, 331
Acridone, 333
Acridylanthraquinone, 337
Acridylmethylol, 335
Acriflavine, 338, 339
 preparation of, 336
Acyclic compounds (*see* Open-chain compounds)
Adamkiewicz test, 350
Addition, of alkyllithium to pyridine, 195
   to quinoline, 298_{2f}
 of amine to anil, 337

Addition, of hydrazine to isothiocyanate, 374
    to triple bond, 374, 375
  of hydrazoic acid to unsaturated systems, 369, 467
  of hydrochloric acid to thiocyanate, 366, 378
  of phenylisothiocyanate, 380
  of hydrogen cyanide to chalcone, 343
  of hydrogen sulfide to thiocyanate, 378
  of hydroxyl amine to benzoxazole, 404
    to 4-methylthiazole, 404
  of phenylnitromethane to double bond, 377
  of sodium amide to phenanthridine, 342
    to pyridine, 194
    to quinoline, 276
    to thiazole, 404
  of water to cyanamide, 383
    to double bond, 139
    to thiocyanate, 378
    to triple bond, 139
1,3-Addition, 144
  to aldonitrones, 198
  with diazo compounds, 369
  to furoxans, 417
  to nitrones, 144
  with ozone, 372
1,4-Addition, in Diels-Alder reaction, 236
  to furan, 7
  of sodiomalonate to quinones, 163
    to vinylnitrile, 289
Adenine, 494, 496
Adenosin, 513
Adrenaline, 453
Aglucone, 163
Agranulocytosis, caused by pryamidone, 444
Alanine, β-(4-methylthiazolyl-5)-, 428
Aldehydes, condensation, with N-allylrhodanine, 431
    with coumaranone, 26
    with hydantoin, 458
    with indoxyl, 123
    with oxindoles, 120
    with N-phenylrhodanines, 431
    with rhodanines, 430
    with thioindoxyl, 52
  preparation of, from acid chlorides by hydrogenation, 212, 458
    from acyl-1,2,-dihydroquinaldonitriles, 293
Aldehydes, preparation of, from α-amino acids, 132, 312, 313
    from anils by hydrolysis, 213, 331
    from benzyl chlorides, 516
    from dichlorides by hydrolysis, 212, 277
    from esters, 428
    from glyoxylic acids, 29, 114
    from hexamethylene tetramine and phenols, 516
    from hydrogen cyanide, hydrochloric acid with aromatic compounds, 16, 22, 29, 30, 63
    from α-hydroxy acids, 153, 162, 451
    from α-keto acids, 29
    from levulinic acid, 451
    from piperidines by oxidation, 241
    from selenium dioxide and picolines, 212
      and methylquinolines, 284
  reaction of, with azides, 371
    with diazomethane, 369
  synthesis, of azlactones with, 29, 114, 421
    of hydantoins with, 460
Aldonitrones, addition to, 198
Aliphatic compounds from heterocyclic compounds (*see* Open-chain compounds)
Alizarin blue, 262
Alkaloids, areca nut, 251
  belladonna, 247
  berberine, 314, 318
  bisisoquinoline, 314
  cactus, 314
  cocaine, 249
  curare, 319
  cusparine, 293
  emetine, 356
  ergot, 452
  galopine, 293
  harmine, 348
  hemlock, 244
  isoquinoline, 312
  lobelia, 252
  lupine, 253, 358
  morphine, 314
  norsalsoline, 313
  opium, 315
  papaverine, 314
  pelletierine, 251
  phenanthridine, 314

Alkaloids, pomegranate bark, 251
  purine, 493
  quina, 286
  tobacco, 217
  yohimbine, 349
Alkoxycinchoninic acid, 286
Alkylation, by Ladenburg reaction, 199, 200
  with lithium alkyls, 195
  with sodium alkoxides, 63, 415
Allantoic acid, 461
Allantoin, 460
Allantoinase, 460
Allergy, histamine and, 453
Alloimperatorin, 163
Allomerization, 95
Allonal, 491
Alloxan, 490
  acidity of, 488
  condensation of, with benzene, 491
    with rhodanine, 430
Alloxazine, 497
Alloxazine-adenine-dinucleotide, 497
o-Allylphenol, rearrangement of, 21, 37_8
Alstonine, 349
Aluminum oxide, as catalyst in preparation, of olefins, 9
    of thiophene compounds, 40, 45
Amarine, 450
Amidine, cyclic, 405
  formation of, 366, 462
Amination, 194
  of pyridine, 194
  of quinoline, 276
  of thiazole, 404
Amines, diagnostic method for primary, secondary, and tertiary, 232
  β-ethanol-, 478
  hydroxy-, preparation of, 269
    test for, 282
  β-hydroxyethyl-, 452
  β-phenylalkyl, 302
  physiological activity of, 453
  preparation of, by ammonolysis of halogen compounds, 209, 239
    by reduction, of nitriles, 233, 234, 237
      of oximes, 238
    by reaction, with acetoacetates, 265
      with dibromopentane, 232
  reaction of, with cyanamide, 383
    with cyanogen bromide, 383
Amines, secondary, elimination of alkyl groups from, 106
    preparation of, 503
  β-substituted ethyl, 250, 419, 429. 453
  γ-substituted propyl, 250
  tertiary, betaines from, 196
    degradation of, 308
    oxidation to N-oxides, 316
      (*See also* N-oxides)
    reaction with cyanogen bromide, 240
    use in Mannich reaction, 243
Amino compounds (*see* under Acids, Acridines, Phenols, Pyridine, Quinoline)
Amino group, diazotization of, 413
  effect of, on substitution reactions of pyridine, 194
    on substitution reaction of thiazole, 413
  position and reactivity of, 413
  protection of, by carbobenzoxy radical, 454
Aminoantipyrine, 446
μ-Aminochromidan, 184_{10}
Ammonium dithiocarbamate, 429, 432
Ammono-aldehyde system, in azoles, 404
  in indoles, 110
  and lability of carboxyl groups, 412
  in pyridine, 191, 194
  in quinoline, 276, 277
  and reactivity, of halogen atoms, 204
    of methyl groups, 277, 331, 411, 485
    of methylene group, 501
Ammonolysis, of chloropyridines, 209
  of chloropyrimidines, 485
  of chloroquinolines, 282
Amytal, 491
Anabasine, 219
Analgesic action, of trigenin, 444
Anesthetics, local, 13, 434, 440
  of morpholine compounds, 478
Anhalamine, 314
Anhalonidine, 314
Anhydro-o-aminobenzaldehyde, 271
Aniline, first preparation of, 135
  in Skraup synthesis, 262, 280, 355
Anilinopyrine, 444
Anserine, 454
Anthelmintics, 251, 480
Anthocyanins, 164
Anthoxanthins, 166

Anthracene, and naphthotriazoles, 397
  similarity of heterocyclic compounds to, 397
Anthranil, 363, 425
  chloro, 388
  3-methyl, 388
  odor of, 388
  3-phenyl, 388
Anthranils, 392
  preparation of, 386, 425
Anthrazine, 511
Anthrazolines, 345
Antifebril action, of antipyrine, 439, 443
  of melubrin, 444
Antioxidant, 9,9-dimethylacridine as, 340
Antipyrine, 439, 443
Antipyrine red, 446
Antiseptic activity, of acridine compounds, 338
Apiginin, 170
Apocyanines, 294
Apomorphine, 317
Aposafranine, 509
Arecoline, 251, 455
Argenine, 453
Asterin, 166
Atabrine, 340
Atophan, 286
Atropine, 247
Azabicycloheptane, 237
Azabicyclononane, 237
Azabicyclooctane, 230
Azanthraquinone, 355
Azaporphyrins, 95
Azepines, 231
5-Azepotetrazole, 372
Azines, 476
  synthesis of, 476
Azlactones, 421
  incipient, in penicillin, 428
  preparation of α-amino acids with, 428
    of α-keto acids with, 175
    of pyruvic acids with, 30
  synthesis with, 29
  synthesis of histidine with, 453
    of isoquinolines with, 305
    of tryptophan with, 114
Azoles, addition reactions of, 404
  basicity of, 405
  boiling points of, 380
  boiling-point relations in, 389
  bond fixation in, 391
Azoles, chemical properties of, 399
  methiodides, decomposition of, 407
    naming and numbering of, 362
  preparation of, from azides, 369
    from azo compounds, 369
    from condensed systems, 377
    from diazo compounds, 369
    from 1,4-dienol systems, 364
    from hydrazines, 378
    from α-substituted ketones, 366
  substitution reactions in, 399
  synthesis of, comparison of, with azines, 476
Azolidines, 363
Azolines, 363
Azolones, acidity of, 488
  condensation products of, 444
  preparation of, 378
  reactions of, 415

B

Bacterostatic index, of aminoacridines, 339
Banisterine, 348
Barbitol, 491
Barbiturates, 487
  comparison of, with thiazolones, 432
  physiological action of, 489, 494
  synthesis of, and comparison with azines, 477
  theory of action of, 460
Barbituric acid, 487
  acidity of, 487
  dibromo, 490
  5,5,diphenyl, 491
  5-nitro, 490
Basicity, of acridines, 339
  of azoles, 405
  of carbazoles, 141
  effect of, on methylation, 402
  of hydroxypyridines, 221
  of piperidine, 243
  of pyridine, 405
  of pyridoxime, 221
  of sulfa compounds, 428
  of thiazole, 405
Bebeerine, 320
Beckmann rearrangement, 422
  of dioxime of lobeline, 252
  preparation of amines by, 303
  ring enlargement by, 231, 254, 274, 341, 372, 499

Benz group, effect of, on melting point, 392, 506
    on reactivity of furan, 23
Benzaldehydes, from benzyl chloride, 516
  o-hydroxy, 516
Benzazoles, naming and numbering of, 363
  physical properties of, 386
  preparation of, from anilines, 381, 384
    from *o*-halogenobenzenes, 383
    from *o*-nitrobenzenes, 386
  solubility of, in water, 386
  synthesis of, 381
Benzene-pyrimidine systems, 484
Benzidine rearrangement, in preparation of carbazole, 101
Benzimidazole, 463
Benzimidazoles, benzoid character of, 395
  preparation of, 382
  synthesis of azines and, 476
1,2-Benzisoazole, 363
  preparation of, 385
Benzisothiadiazole, 363
1,2-Benzisoxazole, 3-phenyl-, 388
2,1-Benzisoxazole (*see* Anthranil)
Benzo-1,2,3,4-bisthiazole, 2,6-diphenyl-, 438
Benzo[*c*]cinnoline, 481
Benzoflavine, 336, 338
Benzofuran, 20
  benzoid character of, 395
Benzofuran compounds, 26
  naming and numbering of, 20
  reactions of, 23
  ring opening of, 25
Benzofuran-2-carboxylic acid, 23
Benzoid properties, 394
Benzonitrile, preparation of, 514
Benzo-γ-pyrones, 164
Benzopyrylium salts, 167
Benzo[*f*]quinoline, 328
Benzo[*h*]quinoline, 328
Benzoselenazole, odor of, 387
Benzothiadiazole, 382
Benzothiazole, 432
  2-amino, 385, 433, 434
  benzoid character of, 395
  2-chloro, 432
  4,6-dimethyl, 388
  2-ethyl, 388
  2-mercapto, 437
  methyl, 388
Benzothiazole, 6-nitro, 388
  odor of, 387
  2-phenyl, 388, 433
  preparation of, 382, 385
  2-*p*-tolyl, 433
Benzotriazole, naphthoid character of, 395
  preparation of, 382, 384
Benzoxathiazole, 363
Benzoxazine, 477
Benzoxazole, addition of hydroxylamine to, 404
  2-chloro, 388
  5-chloro-2-methyl, 388
  2,5-dimethyl, 388
  2-methyl, 388
  odor of, 388
  preparation of, 382, 477
  trimethyl, 388
Benzoxazole-4-arsenic acid, 1-amino-, 420
Benzoyleneurea, 499
Berberine, 319
Berberonic acid, 350
Bergapten, 163
Betaines, 196
Bicyclic systems, naming and numbering of, 229
  synthesis of, 235
Bicyclothianium compounds, 237
Bilirubin, 79
  pyrroles from, 70
Biogenic synthesis, 271, 302, 312
Biotin, 456
  synthesis of, 457
Bispidine, 260_{13}
Bispiperidinum compounds, 256
Boiling points, relationships of, in azoles, 389
  very high, in compounds, 354, 392, 433
Bonds, static or fixed, in azoles, 391, 411
    in isoquinolines, 306, 307
    in quinolines, 278
Bone oil, composition of, 185
Brazan, 35
Brazilin, 175
Brazilinic acid, 175
Bromination, of pyridine, 193
  reagents for mild, 42
  of thionaphthenes, 49
Bromindigo, 138
Bromo group, activation of, by ammono aldehyde, 208

Bromo group, activation of, by nitro, 390, 393
  elimination of, by reduction, 412, 417
  replacement of, by chloro, 48
Bromocoumaranone, 24
Bufotenine, 118
Butin, 170

C

Cadaverine, 452
Caffeine, 493, 494
  synthesis of, 494
Callistephin chloride, 165
Camphidine, 261$_{17}$
Cancer-producing compounds, 341
Cannabinol, 176
Captax, 384, 437
Carbazole, 141
  dibenzo-, 101
Carbazole yellow, 142
Carbenium ion, 167
Carbindigo, 311
Carbobenzoxy radical, 454
Carbocyanine, 295
Carboindogenide, 415
Carbolines, 346
Carbon chain, expansion of, 232
Carbonium ion, 167
2-Carbostyril, 276, 281
  1-hydroxy-, 269
  4-methyl-, 265
4-Carbostyril, 2-methyl-, 265
Carboxyl group, activated by ammono aldehyde, 214
  conversion of, to azide, 454
    to methyl, 153
    to nitrile, 221
  elimination of, by mercuric chloride, 7
  protecting influence of, 6, 9
  replacement of, by amino group, 452, 502
    by iodine atom, 7
    by mercuric chloride group, 6
    by nitro group, 44
  stability of, in azoles, 412
Carboxylic acids, preparation of, from azlactones, 30, 175, 428
    from rhodanine and aldehydes, 431
    of tertiary, 12
Carnosine, 454
Catalase, 87
Cerebrosidase, 463
Chalcones, 169, 170
Chavicine, 244
Chelation, in euxanthones, 178
  in imidazole, 402
  in salicylaldoxime, 423
Chelerythrine, 342
Chelidonic acid, 150, 154
Chelidonine, 342
Chiniofen, 282
Chloralantipyrine, 444
Chlorination, moderate, reagents for, 43
Chlorins, 84, 94
Chloro group, replacement of, by amino, 209, 485
    by thiocyano, 368
Chloroketones, preparation of azoles from, 366
    of furans from, 3
    of pyrroles from, 59
Chlorophyll *a*, alkali degradation of, 88
  degradation of, 93
    by hydriodic acid, 90
  porphyrins from, 88
  structure of, 92, 94
Chlorophyll *b*, 92
Chlorophyllide, 92
Chloroporphyrin, 91
Chlorosulfonic acid, as sulfonating agent, 44
Chromanochromanone, 172
Chromans, 158
Chromenochromones, 174
Chrysaniline, 335, 338
Chrysanthemin, 166
Chrysin, 170
Ciba lake red B, 135
Cincholoiponic acid, 289
Cinchonidine, 288
Cinchonine, 288
Cinchoninic acid, 285
Cinchophen, 286
Cinchotoxine, 289
Cinnoline, 481, 506
Cobalt, complex compounds, 439, 443, 463
Cocaine, 249
  substitutes for, 250
Cocarboxylase, 498
Codehydrogenase I, 496
Codehydrogenase II, 497
Codeine, 318

Coenzyme R, 458
Collidines, 185, 206
Colors, in autumn foliage, 167
    (*See also* Dyes)
Columbia yellow, 433, 434
Comanic acid, 155
Comenamic acid, 224
Comenic acid, 155
  pyrolysis of, 150
Compral, 444
Conhydrine, 246
Coniceine, 230
Coniceines, 245, 246
Coniine, 236, 244
Conyrine, 206, 243, 245
Copellidine, 243
Copelline, 243
Coproporphyrin, 84
Copyrine, 353
Copper, complex compounds, 136, 443, 451, 454
Coramine, 214
Cotarnine, 324_{10}
Coumalic acid, 149
Coumalin, 149
Coumaran, 20
  2,4,6,7-tetramethyl-5-hydroxy, 30
Coumarandione, 26
Coumaran-3-one, 20, 26
Coumaranones, 21
Coumarins, 161
Coumarone, 2-aldehydo-, 29
  discovery of, 20
    (*See also* Benzofuran)
3-Coumaronylacetic acid, 29
Creatinine, 462
Cryptocyanine, 295
Cryptopine, 316
  structure of, 323_8
Cryptopyrrole, 69
Cumar resins, 25
Cupreine, 288, 291
Curare, 319
Cusparine, 293
Cyameluric acid, 516
Cyanidin, 165, 166
Cyanin dyes, 118, 294
  in benzoxazole series, 420
  in indole series, 119
  in isoquino[2,1-*c*]quino[2,1-*f*]pyrimidine, 355
  in quinoline series, 294
  in quinoxaline series, 507
  in thiazole series, 435
Cyanogen bromide, ring opening with, 240
Cyanuric acid, 515
Cyanuric triazide, 515
Cyaphenine, 450, 514
Cyclooctatetrene, 260_{14}
Cyclopropane, 424
Cytisine, 357
Cytochrome *c*, 87
Cytosine, 492, 496
  5-methyl, 492

D

Decarboxylation, over quinoline and copper, 71
  at reduced pressure, 502
Deguelin, 173
Dehydroacetic acid, 155
Dehydrogenation, of amino acids, 132
  over nickel, 45, 190
  over palladium, 105, 190, 348
  by platinum, 45, 190, 218
  with silver acetate, 219
  with sulfur, 176, 218
  with zinc dust, 190, 219
Dehydrorotenone, 174
Dehydrothiopseudocumidine, 434
Dehydrothiotoluidine, 384, 433
Dehydrothio-*m*-xylidine, 434
Delphinidin, 165
Deoxyeseroline, 117
Derissic acid, 173
Dermititis, caused by benzothiazole, 433
Derric acid, 173
Derrin, 172
Derritol, 172
Desoxophylloerythrin, 91
Desoxyribonucleic acid, 496
Desoxyvasicine, 501
Deuteroporphyrin, 91
  conversion of, to protoporphyrin, 99_9
Diacetylacetone, conversion of, to pyrone, 151
Diacridonyl, 333
Dial, 491
Dialkylthiazolones, 432
Dialuric acid, 491
Diaminophosphine, 338
Diamorphine, 318

Diaphoretic, pilocarpine as, 455
Diazaanthracene, 346
Diazacarbazole, 358
Diazamercurole, 362
Diazines, 503
Diazo oxides, 284
Diazoalkanes, addition to carbonyl groups, 285
Diazoles, naphthoid character of, 395
  substitution in, 402
Diazomalonanilide, 466
Diazomethane, 369
Diazonium group, ring closure with, 33, 34
Diazotization, of anthranils, 426
Dibenzodiazapyrene, 356
Dibenzo[*b*,*f*][1,5]diazocine, 500
Dibenzofuran, 32
Dibenzothiophene, 53
Dibenzoylethylene, trans-, 32
Dibromides, alkylene, from pyrroles, 67
    from piperidine, 242, 259_{4a}
Dibromin, 487, 490
Dicyanamidazide, 411
Dienes, preparation of thiophenes from, 40
Dienols, preparation of azoles from, 364
    of furans from, 3
    of thiophenes from, 40
Dihydroacridine, 333
Dihydroazoles, stability of, 394
Dihydrobenzenes, stability of, 394
Dihydrofurans, 174
Dihydroimidazoles, 394
Dihydrooxadiazole, 370
Dihydrooxatriazoles, 371
Dihydrophenanthridine, 342
2,3-Dihydrophenylindole, 105
Dihydropyran, 149
Dihydropyrindene, 299_{13}
Dihydroquinicinols, 292
Dihydroquinine, 300_{21}
Dihydrotriazoles, 394
Dihydro-1,2,3-trioxole, 372
Diindolyl, 119
Diindoxyl, 123
Diisatogen, 139
α,β-Diisoxazoyl ketone, 421
1,4-Diketones, cis unsaturated, 12
  preparation, 3
    of furans from, 3
    of pyrroles from, 57
Diketopiperazines, 504
Dilituric acid, 487, 490
Dimethylanolobine, 325_{14}
Dimethylergoline, 352
Dinitriles, 190
Diodrast, 224
Diothane, 250
Dioximes from furoxans, 410, 464
Dioxindole, 126
  preparation of, from isatin, 100
Diphenacyl, conversion of, to furans, 9
Diphenyl ketones, conversion of, to acridones, 329
Diphenylamines, conversion of, to acridines, 329, 334
2,6-Diphenylbenzo-1,2,3,4-bisthiazole, 438
Diphenylene oxide, 33
  reactions of, 33
    (*See also* Dibenzofuran)
Diphenylhydantoin, 380
Diphenylmethanes, conversion of, to acridines, 329
Diphosphopyridine nucleotide, 497
Dipyridyls, 195, 215
  preparation of, from phenanthrolines, 345
α, β′-Dipyridyls, 219
Dipyrrylmethenes, 76
Dipyrroles, 67
Dipyrromethanes, 75
Dithiastibole, 364
Diurein, acetylene, 458
Dyes, acridine, 335, 338
  acridine red, 181
  alizarin blue, 355
  alizarin orange, 355
  from aminoantipyrine, 446
  antipyrine red, 446
  azo, 434, 435
  binschelder's green, 482
  brazilwood, 176
  brilliant phosphine yellow, 338
  brilliant phosphino immino, 338
  capri blues, 482
  chloramine yellow, 434
  ciba lake red B, 135
  ciba scarlet G, 52
  columbia yellow, 433
  cyanine, 119, 294, 355, 420, 435, 507
  dimethylaminophosphine, 338
  eurhodines, 508

Dyes, gallocyanines, 482
  from histidine, 453
  indamines, 482
  indanthrene blue R, 511
  indanthrene yellow R, 356
  indian yellow, 178
  indophenol, 482
  ingrain, 434
  lauth's violet, 483
  mauve, 508
  Meldola's blue, 479
  methylene blue, 479, 480, 483
  methylene blue GG, 480
  neutral red, 483, 507
  oxazine, 479, 482
  oxindigo, 26, 27
  phenazine, 507
  phenonaphthoxazine, 480
  porphyrindin, 463
  primulin, 433
  pyrazole blue, 445
  pyrazolone, 448
  quinoline red, 355
  rhodamines, 182
  rosinduline, 509
  safranine, 483, 509
  safranole, 483
  simple neutral red, 507
  thiacyanine, 435
  thioindigo, 51
  thioindigo scarlet R, 52
  thionol, 483
  toluyleneroth, 507

E

Ecgonine, 249
Ehrlich's test, 68, 106
Eldoral, 491
Elliptone, 364, 174
Elsholtzione, 16
Embutal, 491
Emetine, 356
Endings of words, 476
  -azine, 476
  -azole, 362
  -epine, 476
  -ete, 476
  -ole, 363, 476
Enimization, in Fisher-indole synthesis, 101
  in imidazoles, 401
Enimization, in indoles, 104, 105
  in pyrazoles, 400
  in pyrroles, 62
Enzymes, allantoinase, 460
  catalase, 87
  cerebrosidase, 463
  cocarboxylase, 498
  codehydrogenase I, 496
  codehydrogenase II, 497
  coenzyme R, 458
  indimulsin, 124
  papain, 463
  peroxidase, 87
  pyruvic dehydrogenase, 498
  urease, 463
Eosine, 182
Eosines, 181
Epindolines, 351
Epiquinine, 288
Epiquinoline, 288
Ergine, 351
Ergonovine, 351
Ergot, 350, 452
Ergotamine, 351
Ergotoxime, 351
Eriodictyol, 170
Erythroapocyanine, 295
Erythrosin, 182
Esculetin, 162
Eserine, 116
Ether system, influence of, in azoles, 386
    in furan, 11
  1,4-reduction of vinyl, 24
Ethyl isatogenate, 125, 139
Eucotropine, 247
Euflavine, 338
Eumadrine, 247
Eumarcon, 491
Euparin, 366
Eurhodines, 508
Euxanthic acid, 178
Euxanthone, 178
Evipal, 491
Evodiamine, 501
Exhaustive methylation, 60, 307
  in curare, 321
  in isoquinoline compounds, 317
  in lobeline, 252
  in pyridine compounds, 201
  in tropine, 249

F

Ferripyrine, 444
Ferroin, 344
Fibroin, 506
Fisetin, 170
Fish poisons, 163
Flavaniline, 294
Flavanols, 164
Flavanthrine, 355
Flavazole, 513
Flaveosine, 336
Flavicide, 338
Flavine, 338
Flavins, 511
Flavones, 169
Flavonols, 169
Flavoprotein, 511
Foliage, autumn, 167
Food, dyes for, 182
Formaldehyde, test for, 318
Fluorescein, 181
Fluorescence, measurement of thiamin by, 487
Free radicals, in reduction of porphyrexide, 463
Fructosazine, 502
Fructose, degradation to dihydroxyacetone, 451
Furan, acylation of, 6
  alkyl, 3
  comparative reactivity with benzene, 6
  comparison with azoles, 389
  2-cyano-5-methyl, 12
  diene character of, 7
  iodo, 5
  metalation of, 6
  β-methyl, 16
  numbering of, 2
  substitution in, 4, 6
Furan compounds, addition reactions of, 7
  amino, 10
  conversion of, to pyrroles, 59
  divinyl ether behavior of, 7, 11
  hydroxy, 10
  mercurated alkyl, 6
  physical properties of, 15
  physiological activity of, 13
  synthesis of, 3
Furanosides, 17
Furazan, 362
Furfural, 2, 13
  5-ω-chloromethyl, 3
  5-ω-hydroxymethyl, 3, 14
  5-methyl, 3
Furfuryl alcohol, 4, 15
  polymerization of, 8
Furfuryl bromide, 4
Furfuryl chloride, 17
  decomposition of, 9
Furocoumarins, 163
Furodiazoles, 365
2-Furoic acid, 4, 15
  5-bromo, 16
  5-bromo-4-isopropyl, 4
  reaction of, with bromine, 9
3-Furoic acid, 16
  2-bromo, 5
Furozans, 416, 464

G

Gallocyanines, 480
Galopine, 293
Gentisen, 179
Glucuronic acid, 178
Glutaconaldehyde, preparation of, from pyridine, 200, 436
Glycine anhydride, 504
Glyoxal, 449
Glyoxaline, 363, 449
Glyoxalpropionic acid, preparation of, from levulinic acid, 452
Gmelin's test, 80
Gramine, 147$_{32}$
Grignard reagent, for anhydrous hydrolysis of ester, 10
  preparation of, from bromodibenzothiophene, 53
    from 3-bromothionaphthene, 51
    from halogeno furan compounds, 17
    from β-halogeno vinyl ether, 25
    magnesium copper alloy for, 25
  reaction of, with acridine, 337
    with aldehydes, 4
    with cyclic anhydride, 32
    with indole, 107, 119
    with a nitrile, 16
    with pyridine, 197
    with quinoline, 276
    with sarcosin anhydride, 505
    (*See also* Reactions, Grignard; Zerewitinov)

Guanine, 494, 496
Guanylhydrazine, 376

H

Halogen, activation of, by ammonoaldehyde, 208
  addition of, to furan compounds, 7
  elimination of, from azines by reduction, 417
    from azoles by reduction, 412
  hydrolysis of, in azoles, 413
Harmaline, 348, 349
Harman, 347–349
Harmine, 348
Heats of combustion, in angular and linear condensed systems, 397
Hem, 84
Hematein, 176
Hematinic acid, 79, 83
Hematoxylin, 175
Hemoglobin, as catalyst in luminescence, 483
  degradation of, to porphyrins, 88
Hemopyrrole, 69
Heroin, 318
Hesperitin, 170
Heteroauxin, 113
  oxygen analogue of, 29
  thiophene analogue of, 51
Hexamethylene tetramine, 513
Hexogen, 516
Hexoses, conversion of, to furfural, 3
  differentiation of, from pentoses, 8
Histamine, 452
  2-thiol, 455
Histidine, 453
Histidol, 453
Hofmann degradation, isolation of intermediate product in, 502
Hofmann's rule, 307
Homopilopic acid, 456
Hopkins-Cole test, 115, 118
Hordenine, 314
Hydantoic acid, ethyl ester, 458
Hydantoin, 458
  diphenyl, 458
  5,5-ethylphenyl, 460
  5-substituted, 459
Hydrazines, preparation of azoles with, 374
s-Hydrazines, preparation of, from pyrazoles, 407
Hydrazoic acid, 1,3-addition of, 369
  formation of azoles with, 369, 467
Hydrocinchonidine, 288
Hydrocupreine, 291
Hydrogenation (*see* Reduction)
Hydrone blue, 142
Hydroquinidine, 288
Hydroquinine, 288, 300_{21}
Hydroxyl amine, addition of, to thiazoles, 404
Hydroxyl groups, in azoles, 414
  reduction of, by phosphorus pentasulfide, 414
Hydroxyphenylthiazone, 481
Hydroxyuracil, acidity of, 488
Hygrine, 261_{18}
Hyoscine, 247
Hyoscyamine, 247
Hypaphorine, 115
Hypnotics, hydantoins as, 460
  theory of action of, 460
Hypoxanthine, 494

I

Idacin, 166
Ikterogen, 74_{11}
Imidazole, 450
  β-aminoethyl, 452
  1,5-dimethyl, 454, 456, 463
  2,4-dimethyl, 450
  4,5-diphenyl, 451
  4(5)-hydroxymethyl, 451
  4(5)-methyl, 450
  triketo, 460
Imidazole-4(5)-carboxylic acid, 451
Imidazole-pyrimidine system, 484
Imidazoles, 449
  acidity of, 405
  boiling points of, 390
  methylation of, 402
  Pauly test for, 454
  preparation of, 364, 404
    and azines, 476
    stability of, 404
  substitution in, 401
Imidazolones, 458
Imidazolylacetic acid, 471_{14}
β-(4-Imidazolyl)proprionic acid, 451

Imine-ketimine system, in imidazoles, 401
  in indoles, 104, 105
  in pyrazoles, 400
  in pyrroles, 62
Imino ether, in preparation of azoles, 375
  reaction of, with ammonia, 366, 462
    with hydrazine, 366, 374, 375
Iminohydrazide, 366
Iminothiadiazolone, 375
Imperatorin, 163
Indalone, 152
Indamines, 482
Indanthrone, 511
Indazole, 363
  5-nitro-3-bromo-2-methyl-, 393
  preparation of, 382, 385
Indazoles, 448
  naphthoid character of, 395
Indene, 25
Indican, 124, 133
Indicators, in electrometric processes, 344
  oxidation-reduction, 481, 510
  pyocyanine, 510
  for titration of rhodanine, 430
Indigo, 132
  analogues of, 138
  aniline by pyrolysis of, 135
  cis- and trans-forms of, 134
  congener of, 354
  derivatives of, 100, 135
  metal complexes with, 136
  oxygen analogue of, 26
  pyrazolone analogue of, 445
  thio analogue of, 51
Indigo white, 134
Indigosol, 134
Indimulsin, 124
Indirubin, 123, 137
Indoflavine, 338
Indogenides, 123, 125
Indole, 106
  3-aldehydo, 112
  α-amino, 111
  bisulfite addition compound of, 106, 110
  2,3-dimethyl, 109
  2-methyl, 107
  3-methyl, 108
  4-methyl, 108
  5-methyl, 108
  2-phenyl, 109
Indole-3-acetic acid, 112
Indole-β-carboxylic acid, 112
3-Indolemethylamine, 112
Indolenine red, 119
Indolenines, 109
Indoles, preparation of, 100
    from dipyrroles, 67
  reactions of, 104
  ring opening of, 105
Indoline, 111
Indolines, 111
Indolizine, 236
  formation of, 205
β-(Indolyl-3)propionic acid, 114
Indophenine test, 39, 46, 129
  in azoles, 400
  in diazoles, 402
  in thiophene, 39
  in triazoles, 402
Indoxazene, 423
Indoxyl, 121
Indoxylic acid, 124
Inosic acid, 513
Insulin, 463
Iodination, of benzene, 43
  of pyrrole, 65
  of thiophene, 43
Iodo substituent, replacement of, by nitro group, 7
Iodol, 65
Iodopyridone compounds, 224
Iopax, 224
Ipral, 491
Iregenin, 171
Iron salts (*see* Metal complexes)
Isatan, 128
Isatide, 126, 128
  structure of, 145_{26}
Isatin, 126
  condensation of, with rhodanine, 130, 471_{16}
  indazoles from, 383
  in indophenine reaction, 39, 46
  oxime, rearrangement of, 499
  quinolines from, 273
  reduction of, 100
  thioindigo dyes from, 52
Isatin-α-anil, 132
Isatinic acid, 129
Isatogen, 139
Isoalloxazine, 512
Isobenzofurans, 31

Isocarbimidindogenides, 125
Isocarbostyril, 311
Isocryptopine, 316
Isocyanine, 295
Isoflavones, 171
Isoimidazole, 362
Isoindigo, 139
Isoindogenides, 125
Isoneoxanthobilirubic acid, 80
Isonitrosocoumaranon, 23
Isopyrazole, 362
Isoquinaldinic acid, 285, 311
Isoquinoline, 311
  1,4-dihydroxy-, 311
  7-hydroxy-, 325$_{13}$
  synthesis of from α-methylisoindole, 341
Isoquinoline alkaloids (*see* Alkaloids)
Isoquinoline carboxylic acid, 311
Isoquinoline compounds, 311
  preparation of, 301
  reactions of, 306
Isothiazole, 362
Isotubaic acid, 28
Isoxazole, 5-*n*-amyl-, 388
  4-anisyl-3,5-diphenyl, 423
  3,5-dimethyl, 421
  diphenylbenzoyl, 424
  3,4-diphenyl-5-*p*-bromophenyl, 423
  5-*n*-hexyl, 388
  methyl, 421
  3-phenyl, 388
  3-phenyl-5-methyl, 421
  3,4,5-triphenyl, 388, 422
Isoxazole azide, 422
Isoxazole carboxylic acid, 421
Isoxazole-5-azotrinitromethane, 421
Isoxazoles, 421
  boiling points of, 390
  chlorination of, 399
  preparation of, from nitro compounds, 377
  reduction of, 404
  solubility of, in water, 386
Isoxazoline oxides, 424
Isoxazolones, 415
Isozonide, 372

K

Kaempferol, 170
Kairolin, 280
Kathepsin, 463
Keracyanin, 166
Ketimine-enimine system (*see* Enimization, Imimine-ketimine)
β-Keto esters, furans from, 3
  pyrroles from, 57
  hydantoins from, 460
Ketones, α-amino, azoles from, 366
  α-chloro, azoles from, 366
    furans from, 3
    pyrroles from, 59
  cyclic, enlargement of ring by oxime of, 372
  preparation of, from aldehydes and diazoalkanes, 285
    from β-keto esters by hydrolysis, 213
    from nitriles and Grignard reagent, 285
  reaction of, with azides, 371
    with diazomethane, 369
  reduction (*see* Reduction, by hydrazine, by oxalyl chloride, by phosgene)
  α-substituted, in preparation of azoles, 366
  α-thiocyano, azoles from, 366
Knorr's pyrrole, 70, 71
Kojic acid, 153

L

Lachrymators, chloroacetylpyrazole, 440
Lactoflavin, 511
Laudosine, synthesis of, 324$_{9}$
Lelobanidin, 261$_{20}$
Lepidine, 277, 279
Leucopterin, 498
Levulinic acid, α-methyl, thiophene compounds from, 43
  preparation of, from furfuryl alcohol, 8
    from gloxalpropionic acid, 452
    methylthiophene from, 40
Levulinic aldehyde, 239
Liebermann's test, for thiophene compounds, 47
Lithium alkyls, addition of, to pyridine, 195
    to quinolines, 298$_{27}$
Lobelan, 260$_{10}$
Lobelanine, 239
Lobeline, 252
Loipoinic acid, 289

Lophine, 450
Lumiflavin, 511
Lumilactoflavin, 511
Luminal, 491
Luminescence, of luminol, 483
Luminol, 483
Lupelidine, 243
Lupinane, 358
Lupinine, 253
Luteolin, 170
Lutidines, 206
  solubility of, in water, 387
Luvican, 142
Lysergic acid, 351

M

Maggots, allantoin in secretion of, 461
Malaccol, 174
Maleic anhydride, addition of, to furan, 7
    to pyrroles, 65
  reaction of, with benzene and aluminum chloride, 32
    with dinaphthylenethiophene, 45
Malobiuret, 487
Malonic ester, acidity of, 488
Maltol, 153
Malvidin chloride, 165, 166
Mauve, 508
Meconic acid, 155
  pyrolysis of, 150
Melam, 517
Melamine, 515, 517
Meldola's blue, 479
Melem, 517
Melting points, of amino acid anhydrides, 504
  of azoles, 391
  of benzdiazines, 506
  of diazines, 503
Melubrin, 444
Meocyanin, 166
Merbaphan, 490
Mercaptans, preparation of, from thiazoles, 407, 409
Mercapto group, oxidation of, 414, 451
Mercuration, of furan compounds, 5, 11
  of thionaphthenes, 50
  of thiophenes, 45
Meriquinone, 511
Meroquinenine, 289
Mescaline, 314
Mesobilirubin, 80
Mesoetioporphyrin, 84, 88
Mesoporphyrin, 88, 89
  conversion of, to pyrroporphyrin, 99$_9$
Metal complexes and salts, of anserine, 454
  with benzimidazole, 463
  with 1,3-diketones, 157
  with dipyridyls, 215
  with imidazoles, 451
    in preparation of, 366
  with indigo, 136
  with nitrosophenylhydroxylamine, 426
  with *o*-phenanthrolines, 344
  with pyrazines, 503
  with pyrazoles, 439
  with pyrazolones, 443
  with pyridine, 203
  with quinoline-2-aldoxime, 284
  with 8-quinolinol, 281
Metalation, of anisole, 11
  of dibenzothiophene, 53
  of furan, 11
  of thiophene compounds, 45
Metal-halogen interchange, in dibenzofuran compounds, 33
Methyl ethyl ketone, condensation of, with ethyl oxalate, 473$_{27}$
  in Fischer indole synthesis, 267
  in Knorr's pyrrole synthesis, 58, 290
  in quinoline synthesis, 267
  reactivity of, on ethyl side, 267, 290
Methyl group, activation of, by ammono-aldehyde system, 204, 277, 411
    by nitro group, 118
  activity of, in anthrazolines, 346
  condensation of, with aldehydes, 331
  reactivity of, in azoles, 411
    in isoquinoline, 307
Methylation, effect of basicity on, 402
  exhaustive (*see* Exhaustive methylation)
Methylene blue, 480, 483
  (*See also* Dyes)
3,3′-Methylenebis-(4-hydroxycoumarin), 164
4-Methylesculetin, 162
4-Methylgranatonine, 251
N-Methylhomogranatonine, 239
α-Methylisoindole, 341
Methylrubazonic acid, 447
N-Methyltryptamine, 116

Metrazole, 372, 466
Migrainin, 444
Mitycaine, 250
Molozonide, 372
Monomethylphosphine, 338
Morin, 170
Morphine, 317
Morpholine, 477
Murexide, 492
Myosmine, 219
Myricetin, 170
Myristicin, 324$_{10}$

N

Naming, of acridine and related compounds, 326
  of azines, 476
  of azoles, 362
  of bicyclic systems, 229
  of coumarones, 20
  of 3- to 9-membered rings, 476
  of piperidine compounds, 229
  of reduced rings, 476
    (*See also* Furans, Pyrroles, Thiophene, and other classes of compounds)
Naphimidazole, reactivity of, 398
Naphthracridines, 341
Naphthoic acids, preparation of, from furoic acid, 13
Naphthoid properties, 394
Naphthothiazoles, 471$_{12}$
α-Naphthotriazoles, 433
  comparison of, with anthracene, 397
α-Naphthoxazole, 2-methyl-, 420
β-Naphthoxazole, 2-methyl-, 419
2,1-Naphthoxazole, 388
Naphthyridine, 297, 328, 353
Narcotine methiodide, degradation of, 309
Nembutal, 491
Neocyanine, 296
Neonal, 491
Neonicotine, 219
Neotropine, 222
Neoxanthobilirubic acid, 80
Nicotinamide, 497
Nicotine, 217
  oxidation of, 218, 261$_{21}$
    to nicotinic acid, 440
Nicotine, synthesis of, 218, 226$_{8}$
Nicotinic acid, 214
Nicotyrine, 218
Nirvanol, 460
Nitrates, conversion of nitrogen to, 512
Nitration, of furans, 6
  of pyridine, 192
  of thiazoles, 400
  of thiophenes, 43
Nitrile group, reaction sequence for introducing, 16
Nitriles, α-keto-, formation of, 29
  preparation of, from acids, 221
    by dehydration, of amide, 221
      of oximes, 251, 252
    from furazans, 406
    from hydrogen cyanide and chalcone, 343
    from isoxazoles, 406
    from rhodanines, 431
Nitro group, activating influence of, 393
  protecting influence of, 9
  replacement by, of methyl, 64
    of other groups, 64
Nitroacridines, 333
Nitrogen atom, configuration of, 257
Nitroguanidine, in preparation of aminotetrazoles, 376
Nitrones, 198
  addition reactions of, 198
  of isoxazoles, 425
  preparation of, from nitroso compounds, 371
Noctal, 491
Nor-, prefix, 348
Norharman, 348
Norlupinane, 230, 253, 254
  synthesis of, 254
Norsalsoline, 313
Nostral, 491
Novalgin, 444
Novasural, 490
Novatropine, 247
Novocaine, 250
N-oxides, in furoxans, 416
  in porphyrexide, 462
  in pyridine compounds, 197
  in synthesis of cryptopine, 316
Nucleic acids, 496
Numal, 491

Numbering, in acridines, 326
  in azoles, 362
    (*See also* under title of different compounds)
Nupercaine, 250, 286

O

Octahydroindolizine, 230
Octahydropyrindole, 230
Octahydropyrrocoline, 230
Octahydroquinolizine, 230, 254
Odors, of azoles, 387
  of 2-phenylbenzothiazole, 433
  of 2-phenyl-5-methyltetrazole, 466
Oenin, 166
Olivetol, 176
Open-chain compounds, from azoles, 406, 471_{10}
  from furan compounds, 5, 8, 12, 13
  from hydantoins, 459
  from imidazoles, 455
  from isoxazoles, 406
  from piperidines, 240, 260_{15}
  from pyridines, 201, 436
  from pyrroles, 67, 71
  from rhodanines, 430
Opsopyrrole, 69
Orcinolphthalein, 182
Oreoselone, 163
Orienting influence, in azoles, 400
  in furan compounds, abnormal, 4
  in furans, 11
  in thiophene compounds, 43
Oroflavin, 511
Ortal, 491
Overton-Meyer theory, 489
Oxacyanines, 420
Oxadiazoles, 362, 464
  boiling points of, 390
Oxalylindigo, 135
1,2-Oxaphosphole, 3,5-diphenyl-2-trichloro-, 468_{30}
Oxathiaphosphole, 362
Oxathiazole, 362
Oxazines, 477
Oxazoles, 418, 419
  alkyl, 380
  boiling points of, 390
  dimethyl, 418
  4,5-dimethyl-2-phenyl, 388
  diphenyl, 418
Oxazoles, methyl phenyl, 418, 471_{12}
  phenyl, 418
  preparation of, from amino acids, 380
    from protein, 381
  reduction of, 404
  resistance of, to oxidation, 410
  triphenyl, 418
Oxazolines, 419
Oxidation, by air, of chlorophyll, 94
    of hematoxylin, 176
    of indigo during sublimation, 137
    of an indole methiodide, 109
    of indoxyl, 123, 137
    of leucoindigos, 134
    of phylloerythrin, 90
    of reduced porphyrins, 83
  by arsenic acid, in Skraup synthesis, 263
  by barium permanganate, of N-methylcytisine, 357
    of methyl ether of pyridoxime, 221
  by benzoperacid, of a pyridine, 197
    of a tertiary amine, 316
  by bromine, of furan compounds, 5, 9
    of dipyrrylmethane, 76
    of isopropyl group, 5
    of piperidines, 190
  by bromine and silver oxide, 5
  by calcium permanganate, of naphthalene, 482
  by chloranil, of dipyrrylmethane, 76
  by chlorine, of amino group, 433; 434
    of oxindole, 121
    of thiocyanates, 486
  by chromic acid or anhydride, of alcohols, 249, 253
    of benzalbarbituric acid, 490
    of bilirubin, 79
    of dihydropyrazoles, 442
    of lobeline, 252
    of methylquinoline, 285
    of phenanthridine, 342
    of porphyrins, 84
    of pyrroles, 68
    of quinine, 289
    of tropine, 248
    of tropinone, 248
    of vitamin E, 160
  by cupric acetate in formation of imidazoles, 366
  by dichromates, of acridine, 333
    of aldehydes, 4

Oxidation, by dichromates, of dibenzothiophene, 53
  of harmaline, 349
  of naphimidazole, 398
  of naphthatriazole, 397
  of quinolizine, 236
 by ferric chloride, of acridanes, 329
  of dipyrromethanes, 76
  of hydroquinone, 71
  of indoxyl, 123
  of tryptophan, 114, 349
  of yohimbine, 350
 by ferricyanides, of acridanes, 329
  of acridinium hydroxide, 331
  of hydrazide, 375
  of pyridinium hydroxide, 199
  in thioindigo dye formation, 51
 by hydrogen peroxide, of aminopyridines, 211
  of 1,4-dihydroxyisoquinoline, 311
  of imidazoles, 410
  of indoxyl, 123
  of isatin compounds, 130
  of ozonides, 71
  of piperidine, 241
  of pyruvic acids, 120
  of substituted pyrazines, 502
  of tetrahydromethylderritol, 173
  of tetrahydroquinoline, 280
  of thiophenol, 215
 by hypochlorous acid, of quinoline, 275
 by iodine, of rotenone, 173
 by nitric acid, of acridanes, 329
  of alloxantin, 490
  of dihydropyridines, 187
  of hydroxymethylimidazole, 451
  of imidazole, 410
  of lysergic acid, 351
  of mercapto group, 414
  of nicotine, 440
  of quinolizine, 236
  of uric acid, 462
 by nitro compounds, of piperidines, 190
  in Skraup synthesis, 263
 by periodic acid, of desthiobiotin, 457
 by peroxides, of trithianes, 517
 by persubstituted halogen compounds, 490
 by persulfate, of aminopyridine, 211
 by phenylhydrazines, of anils, 102
Oxidation, by potassium chlorite, of thiazoles, 410
  of uric acid, 490
 by potassium permanganate, of acridines, 333
  of acrylic acid, 287, 335
  of alkylthiophen, 43
  of anabasine, 219
  of aryl group, 34
  of azoles, 377
  of benzene system, 201
  of benzoylpiperidine, 241
  of berberine, 319
  of brazilin derivative, 175
  of carbostyrils, 281
  of cyanine dyes, 295
  of dehydrorotenone, 173
  of hydroxyalkyl groups, 5
  of indole compounds, 105, 109
  of isoquinoline compounds, 315
  of methyl groups, 34, 340
  of naphthalene, 482
  of phenanthrolines, 344
  of piperic acid, 244
  of polyhydroxyanthraquinone, 313
  in preparation of pyrazole carboxylic acid, 442
  of pyridine systems, 201
  of pyronine, 181
  of quinine, 289
  of quinoline, 221, 275
  of substituted pyrazine, 502
  of tetrahydroquinoline, 510
  of tetrazolium salt, 377
  of triarylpyrylium salts, 157
  of trithianes, 517
  of tubocurare-type compound, 320
  of uric acid, 461
 by selenium dioxide, of dimethyldipyridyls, 217
  of keto methylene system, 277
  of methylquinoline compound, 298
  of quinaldine, 277
 by silver acetate, of piperidines, 191
 by silver nitrate, of vitamin E, 161
 by silver oxide, of bromo alkyl group, 5
  of piperidinium salt, 256
 by sodium nitrite, of indigosol, 134
 by sulfuric acid, of aminopyridine, 211
  of piperidine, 191
  (*See also* Dehydrogenation)

Oxidation and reduction, intromolecular, 8, 377
Oxidative cleavage, of azoles, 410
Oximes, configuration of, 422
  ring enlargement from cyclic, 231, 273, 342, 372
Oxindigo, 26, 27
Oxindirubin, 27
Oxindole, 120
  formation of, from isatin, 100
Oxonium salts, 167, 168
Oxyberberine, synthesis of, 324_{12}
Oxygen, replacement of nuclear, in azoles, 411
    in furan, 9
    in pyrones, 151
Oxytryptophan, 116
Ozone, structure of, 372
Ozonides, 372
Ozonization of benzofurans, 24

Pantocaine, 250
Papain, 463
Papaverine, 315, 324_{11}
Paper, safety, 434
Parabamic acid, 462
Parpevoline, 243
Parvolines, 186, 206
Pauly, color test, 454
Peganine, 501
Pelargonidin, 165, 166
Pelletierine, 251
Pellotine, 314
Penaldic acid, 429
Penicillamine, 429
Penicillin, 428
Penicilloic acid, 429
Pentamethylene dibromide, synthesis of, 201
Pentamethylene tetrazole, 372
Pentarsenole, 365
Pentazole, 362
Pentobarbital, 491
Pentosans, conversion of, to furfural, 13
Pentoses, conversion of, to furfural, 3
  differentiation of, from hexoses, 8
Pentothal, 491
Peonidin, 166
Peppers, synthetic, 244
Perabrodil, 224
Perbromides, of azoles, 399
  of pyridine, 400
  of pyrone, 150
  of thiazole, 400
Percaine, 286
Pernocton, 491
Peroxidase, 87
Peucedanin, 163
Phanodorn, 491
Phase test for chlorophyll, 95
Phenacylacetone, furan compounds from, 9
Phenanthraquinone, condensation of, with rhodanine, 430
Phenanthrene, comparison of, with naphthotriazoles, 397
Phenanthridine, 341, 342
  numbering of, 327
  preparation of, by Pictet and Hubert's method, 353
Phenanthridone, 342
Phenanthrolines, 328, 343
  o-, complex, with ferrous chloride, 344
Phenanthroxazole, 2-phenyl-, 419
Phenazines, 507
Phenhomazine, 500
Phenobarbital, 491
Phenolisatin, 129, 491
Phenolphthalein, analogue of, 129, 491
  conversion of, to isobenzofuran, 32
Phenols, preparation of *o*-amino, 407
  test for, 446
Phenonaphthoxazone, 480
Phenothiazine, 480
Phenotripyridine, 354
Phenoxazines, 478
Phenylazide, 1,3-addition of, 369
Phenylcoumalin, 152
Phenylhydrazones, conversion of, to indoles, 101
N-Phenylpyridine, from N-benzylpyrrole, 341
Phenylselenoxanthydrol, 184_8
Pheophorbide, 95
Pheoporphyrin, 90, 94
Phorbins, definition of, 94
  formation of, 92
Phosphine, 335
Photoflavin, 511
Photographic process, antihalation agent for, 448
  filter layer in, 445

- Photographic process, sensitizer for, acridine orange as, 337
    - cyanine dyes as (*see* Dyes, cyanine; Cyanin dyes)
- Phthalazine, 481, 506
- Phthalhydrazides, 482
- Phthalocyanines, 96
- Phthalonic acid, 482
- Phyllins, 84
- Phyllochlorin, 95
- Phylloerythrin, 90, 91
- Phylloporphyrin, 88, 89
    - γ-, 90
- Phyllopyrrole, 69
- Physiological activity, of acridine compounds, 339
    - of alkaloids (*see* Alkaloids)
    - of caffeine, 494
    - of dibenzofurans, 35
    - of furan compounds, 13
    - of histamine, 453
    - of nucleic acids, 496
    - of quinoline compounds, 283
    - of thiol group, 455
    - of trigenin, 444
- Physostigmine, 116
- Physostigmol, 116
- Phytyl alcohol, 93
- Picolines, 185, 186, 204, 206
    - solubility of, in water, 386
- Picolinic acid, 213
    - α-, 285
- Pigments (*see* Dyes)
- Pilocarpidine, 456
- Pilocarpine, 455
- Pilopic acid, 456
- Pilosinine, 456
- Pimelic acid, from biotin, 456
    - from furfural, 5
- Pinacolin rearrangement, of dihydroxydihydrouric acid, 461
- Pinacyanol, 339
- Pinacyanole, 296
- Pinaflavol, 339
- Pine-splinter test, in carbazoles, 141
    - in coal-tar distillate, 185
    - with indoles, 106
    - for pyrroles, 68
- Pipecolines, 243
- Piperazine, 504
    - use of, in synthetic paper, 244
- Piperazines, 503, 504
    - from polymerization of thiazolyl chlorides, 429
- Piperidine, 243
    - α-butyl-, 236
- Piperidine compounds, conversion of, to acyclic systems, 260
    - effect of, in preventing oxidation, 243
    - reactions of, 240
    - ring opening of, 240
    - synthesis of, 230
- Piperidinium pentamethylene dithiocarbamate, 243
- Piperidino, 229
- Piperidocoline, 230
- Piperine, 244
- Piperolidine, 230
- Piperonylic acid, 244
- Plasmoquine, 283
- Polyhydroxyflavones, 169
- Polymerization, of 2-alkylthiazolyl chlorides, 429
    - of benzonitrile, 514
    - of coumarone, 25
    - of cyanogen chloride, 515
    - of dihydrobenzofurans, 21
    - of furfuryl alcohol, 8
    - of indene, 25
    - of Schiff bases, 513
    - of thazolyl chlorides, 429
    - of thioformaldehyde, 517
- Polypyridyls, 215
- Porphin, 84, 87
- Porphyrexide, 462
- Porphyrexin, 462
- Porphyrindin, 462, 463
- Porphyrins, 81, 87
    - in bitumen, 92
    - naming and numbering of, 84
    - preparation of, 85
    - reactions of, 83
- Positive pole, effect on reactivity in pyridine compounds, 191, 192
- Prefixes, iso-, 363
    - nor-, 348
- Primuline base, 433
- Procaine, 250
- Proflavine, 338
- Proline, 72
- Proline anhydride, 504
- Prominal, 491
- Prontosil, 364

Proponal, 491
Proteins, coupling of, 453
  determination of sulphydryl group in, 463
  preparation of oxazoles from, 381
Protoetioporphyrin, 88
Protopine, 325_{14}
Protoporphyrin, 87, 88
Pseudoconhydrine, 246
Pseudocumene, 434
Pseudoindoles, 109
Pseudopelletierine, 251
Pseudotropine, 259_7
Pseudouric acid, 487, 495
Pterins, 498
Purine, 493
Purpuric acid, 492
  of pyrazole series, 447
Purpurins, 94
Putrescine, 452
Pyocyanine, 510
Pyramidone, 444
  transformation product of, 447
Pyran compounds, 149
  numbering of, 148
Pyranthone, 356
Pyrazines, 502
  alkyl, synthesis of, 502
  boiling points of, 503
Pyrazole, chloracetyl-, 440
  5-chloro-1-phenyl-3-methyl-, 444
  dimethyl-, 439
  4-nitro-5-(3-pyridyl)-, 440
Pyrazole blue, 445
  reaction of, with ammonia, 447
    (*See also* Dyes)
Pyrazole carboxylic acids, 440
Pyrazole-4-phosphinic acid, 5-chloro-1-phenyl-3-methyl-, 444
Pyrazoles, 439
  acyl, 439
  basicity of, 405
  boiling points of, 390
  stability to acids, 407
  substitution in, 400
Pyrazolines, 440
  tetraphenyl, 415
  triphenyl, 442
5-Pyrazolone, 415
  3-methyl, 415
  1-phenyl-3-methyl-, 443
3-Pyrazolone-4-dimethylamino-1, 5-dimethyl-2-phenyl-, 444
Pyrazolones, condensation products of, 444
Pyrazo[1,2-α]pyrazole, 2,6-dialkyltetraketo-, 379
Pyrazylpyrazolone, 416
Pyrethrum, 174
Pyridazines, β-alkyl, 502
  melting points of, 503
  triamino, 486
Pyridine, amino derivatives of, 208
  bromination of, 193
  chemical reactions of, 191
  complexes with, 203
  effect of salt formation on, 196
  halogen derivatives of, 207, 209
  homologues of, 204
  hydroxy, 211
  melting point comparisons with, 503
  3-methyl, 186
  nitro, 211
  preparation of, from condensed systems, 191
    from α-methylpyrroles, 341
    from piperidines, 190
    from pyrones, 235
  reactions of, with sodium amide, 194
  ring opening of, 199, 200
  solubility of, in water, 386
  synthesis of, 186
Pyridine arsenicals, 223
Pyridine carboxylic acids, 213
Pyridine compounds, in bone oil, 185
Pyridine mercurials, 222
Pyridine sulfonic acid, 215
2,4,5-Pyridine tricarboxylic acid, 350
Pyridine-2-aldehyde, 212
Pyridinium chloride, N-phenyl-β-hydroxy-, 14
N-Pyridinium sulfonic acid, 505
Pyridinoles, 346
Pyridium, 222
Pyridobenzimidazole, 464
Pyrido[2,3-*c*]isoquinoline, 328
Pyridones, 211
Pyrido[2,3-*f*]*m*-phenanthridine, 354
Pyrido[3,2-*b*]pyridine, 328
Pyrido[3,2-*c*]quinoline, 328
Pyridoxine, 221
Pyridylacetylene, 207
Pyridylalkenes, 205, 206

Pyridylnitramine, 211
Pyrimidine, 484
  methyl, 484, 485
  dimethyl, 485
Pyrimidines, 483
  melting point comparisons with, 503
Pyrocoll, 506
Pyrokoman, 150
Pyrolysis, of acridine, 333
  of bone oil, 185
  and preparation, of phenanthridine by, 341
    of pyrazines by, 502
    of pyridines by, 185
  of pyromucic acid, 3
Pyromucic acid, 15
  pyrolysis of, 3
α-Pyrone, 149
γ-Pyrone, 150
  2,6-dimethyl, 151
  2,6-diphenyl, 152
  tetrahydro, 238
    conversion of, to bicyclic compounds, 238
Pyrone carboxylic acids, 153
Pyronine, 181
Pyrousnic acid, 29
Pyrrochlorin, 95
Pyrrocoline, 230
Pyrrodiazoles, 365
Pyrroetioporphyrin, 88
  synthesis of, 99_{10}
Pyrrole blue, 129
Pyrrole compounds, 69
Pyrrole red, 66
Pyrrolenphthalide, 69
Pyrroles, 56
  acidic properties of, 60
  addition reactions of, 65
  amino, 64
  coupling with, 64
  crypto, 69
  hemo, 69
  Knorr's, 70
  methyl, 70
  naming and numbering of, 56
  nitration of, 64
  opso, 69
  phenolic properties of, 60
  phyllo, 69
  pine-splinter test for, 56
  reactions of, 60
Pyrroles, reduction of, 66
  ring opening of, 67
  substitution in, 63
  synthesis of, 56
  tests for, 68
  tetraanisyl, 101
  tetraphenyl, 101
Pyrrolidines, 66, 231
Δ^1-Pyrroline, 66, 71
Pyrropheophorbide, 95
Pyrroporphyrin, 88, 89
  conversion of, to mesoporphyrin, 89, 99_9
Pyruvic dehydrogenase, 498
Pyrylium salts, 156

Q

Quebrachine, 349
Quercitin, 170
Quinaldine, 277, 279
  synthesis of, 263, 271
Quinaldinic acid, 285
Quinazoline, 499, 506
  synthesis of, 477
Quinazolines, 498
Quinazoloneacetic acid, 501
Quindolines, 354
epi-Quinidine, 288
epi-Quinine, 288
Quinine, 287
  comparison of, with pyrazolones, 443
  synthesis of, 290
Quininic acid, 289
Quinoline, 278
  aldehydo, 284
  α-amino, 270
  8-amino-6-hydroxy, 282
  2,4-dihydroxy, 269
  2,3-dimethyl, 267, 333
  homologues of, 278
  hydroxy, 281
  preparation of, from α-methylindole, 341
  reactions of, 275, 278
  synthesis of, 262
  tetrahydro, 274, 280
Quinoline carboxylic acids, 285
Quinoline compounds, preparation of, from isatin and hydantoin, 459
  therapeutic activity of, 283
Quinoline diazooxides, 283
Quinoline yellow (*see* Dyes)

Quinolinic acid, 275
Quinolinofurazan, 284
8-Quinolinol, 281
Quinolizine, 236
Quinones, 1,4-addition to, 163
  addition of phenylazide to, 368
  reduction potential of, 398
Quinosol, 282
Quinoxaline, 502
  odor of, 387
  synthesis of, 476
Quinoxaline cyanines, 507
Quinoxaline-pyrazole systems, 513
Quinoxalines, 506
Quinoxyl, 282
Quinuclidine, 230
  synthesis of, 237, 255
Quinuclidine-2-carboxylic acid, 259

R

Ravenelin, 179
Reactions, Arndt-Eistert, 29, 51, 370
    preparation of acids by, 29
      of homopilopic acid by, 456
  Beckmann rearrangement, in preparation of phenanthridines, 341
    (*See also* Rearrangement, Beckmann)
  Bergmann's protection of amino group, 454
  Bischler and Napieralski, 301
  Chichibabin, 195, 208, 210
  Claisen's condensation, 103
    in synthesis of quinoline, 268
  Clemenson reduction, abnormal behavior in, 254
  Curtius, 115, 341
    with biotin, 457
    with 1,2,3-triazole-5-carboxylic acid, 465
  Curtius-Schmidt, 238
  Dieckmann, 232, 235
  Diels-Alder, with furan, 7
    with pyrroles, 66
    in synthesis of bicyclic compounds, 236
  Friedel-Craft, with acid chloride, 75
    with alkyl chloride and furans, 4, 5, 10
    with anhydrides, 32, 44, 175
    with bromoacetyl chloride, 27
    with chloroacetyl chloride, 165
Reactions, Friedel-Craft, and porphyrins, 83
    in thiophene series, 43
    in xanthone synthesis, 177
  Gmelin's, 80
  Grignard, with azoles, 405
    with benzil, 47
    with coumarins, 168
    with imidazole, 402
    with pyrroles, 61
  Hoesch, 22
  Hofmann, 208, 218, 221
  Jacobsen, 31
  Japp-Klinglemann, in preparation of carbolines, 345
    of harmalan, 349
    of indoles, 102
  Knoevenagel's, 27
    in preparation of pyridine compounds, 187
    use of piperidine in, 243
  Kolbe, 28
  Ladenburg, 199, 200
  Madelung's, 103
  Mannich, 31
    with benzylideneacetone, 442
    intramolecular, 242
    morpholine in, 478
    piperidine in, 243
    synthesis of bicyclic compounds with, 240
    in synthesis of quinine, 290
  Niementowski, 498
  Perkin, with furfural, 5, 28
    effect of pyridine on, 202
    in synthesis of coumarone, 22
      of piperic acid, 244
      of quinoline compounds, 268
  Pfitziner's, 130, 273, 353, 383
  Reformatsky, 237, 238
  Reimer-Tiemann, 516
  Sandmeyer, 127
  Schmidt, 371
  Schotten-Baumann, with aminopyridine, 212
    with azoles, 408
    with 2,6-dihydroxypyridine, 188
    with imidazoles, 408
    with phloroglucinol, 165
    with piperidine, 241
  Widman-Stoerner, 481

Reactions, Wulff-Kishner (*see* Reduction, by hydrazine)
  Zincke, ring opening by, 200
    (*See also* Synthesis)
Rearrangement, of allyl phenyl ether, 21, 31
  of *o*-allylphenol, 21
  Beckmann, 231, 252, 254, 274, 303, 372, 422, 499
    (*See also* Ring enlargement)
  benzidine, 101
  Fries, 21, 31
  of furfurylnitrile, 12
  during ring opening of furfuryl alcohols, 8
  of semidine, in preparation of phenazine, 510
Rectidon, 491
Reduction, by aluminum amalgam, of isoxazoles, 404
  by ammonium sulfide, of dinitroso compounds, 384
    of isatogenates, 125
    of nitro group, 134, 268, 271, 281
    of nitroso group, 444
  during Berginization, 201
  catalytic, over copper chromite, of carboxyl groups, 234
      of indoles, 105
    over nickel, of aldehydes, 4
      of δ-amino ester, 235
      of benzofuran compounds, 24
      of furan compounds, 7
      of indoles, 105
      of isoquinoline, 290
      of nitro group, 346
      of porphyrins, 83
      of pyridines, 195, 201
      of pyrroles, 66, 72
    over palladium, of acid chlorides, 458
      of aldehyde system, 29
      elimination of halogen by, 189, 207, 220, 255, 353
      of furan compound, 7
      of lobeline, 252
      of nitrile, 222
      of olefin system, 293
      of pyridine, 236
    over platinum or platinum oxide, of anabasine, 219
      of benzofuran compounds, 24
Reduction, catalytic, over platinum or platinum oxide, of carbonyl group, 253, 292
      of indole, 105
      of indolizine, 236
      of isoquinoline, 290
      of ketones, 255
      of lupinine, 253
      of *lin.*-naphthatriazole, 397
      of nicotine, 218
      of nitriles, 222, 237
      of nitro groups, 222, 250, 464
      of olefin system, 238
      of porphyrins, 83
      of pyridine system, 195, 292, 352
      of γ-pyrone, 237
      of pyrroles, 66
      of quinazoline, 499
      of quinolizine, 236
      of succinimide, 59
      of tetrahydroisoquinoline salts, 310
      of vinyl ether system, 24
  by chromous chloride, of xanthydrols, 180
  with dextrose, of nitro group, 435
  electrolytic, of diketopiperazine, 503
    of indole, 105, 107
    of isoquinoline salts, 310
    of nitro groups, 269
    of succinimide, 59
  by ferrous sulfate and ammonia, of nitro groups, 118, 268, 270, 346
  by hydrazine and alkoxide (Wulff-Kishner), of ketones, 4, 44, 63, 75, 76, 255
    of nitroso compound, 384
    of phylloerythrin, 90
  with hydriodic acid, of allantoic acid, 461
    of bilirubin, 80
    of chelidonic acid, 154
    of chlorin *c*, 91
    of chlorophyll, 90
    of furoxans, 416
    of ketone compound, 5
    and phosphorus, elimination of halogen atom by, 346, 413
      of ether group, 153
      of keto group, 5
      of nitro group, 269
      of pyrroles, 66

Reduction, with hydriodic acid and phosphorus, of piperidines, 241
    of pyridine, 201
    of β-tocopherol, 161
    of xanthones, 178, 180
  with hydroxyl amine and alkali, of dinitroso compound, 384
  with iron, and acid, of nitro groups, 71, 342, 344
    and alkali, of nitro group, 122
    and water, of nitro group, 33
  with organic acids, in porphyrin synthesis, 86
  with oxalyl chloride, of ketones, 76
  with phosgene, of ketones, 76
  with phosphorus pentasulfide, of hydroxy group in azoles, 414
  with ring opening, 409, 410
  with sodium, and alcohol, of azoles, 404
      of cyclic amides, 116
      of esters, 237
      of ethyl nicotinate, 250
      of nicotine, 218
      of nitriles, 118, 233, 234, 237, 452
      of oximes, 238
      of pyridine, 195, 218, 245, 255, 256
      of pyrimidines, 485
      of succinimides, 59, 66
      of vinylamine system, 114
      (*See also* Reduction, sodium and amyl alcohol, sodium and butyl alcohol)
    and amyl alcohol, of acridone, 333
      of amino acid anhydride, 503
      elimination of halogen atom by, 176
      of lactams, 59
      of lactones, 66
    and butyl alcohol, of lactam, 352
      of lysergic acid, 352
  by sodium amalgam, of α-aminobutyrolactone, 455
    of chelidonic acid, 154
    of coumarins, 162
    elimination of halogen atoms by, 412
    of indoxyl, 123
    of isatin, 100, 126
    of *lin.*-naphthatriazoles, 397
    of olefin bond in α,β-unsaturated acid, 5
Reduction, by sodium amalgam, of olefin system, 253
    of pyrazole blue, 445
    of xanthones, 180
  by stannous chloride, of dinitroso compound, 384
    elimination of halogen by, 277
    of nitro groups, 141, 283
    of oximes, 367, 451
  by tin and acids, of furoxans, 416
    of isatin, 100
    of nitro groups, 33, 112, 210, 268, 269, 344, 386, 435, 463
    of olefin system, 242
    of oxime, 315
    of phenanthridine, 342
    in preparation of anthranils, 425
    of pyrrylpyridine, 218
    of vinyl system, 242
  by titanous chloride, elimination of halogen atom by, 277
  by vanadous chloride, of xanthydrols, 180
  by zinc, and acetic anhydride, of isatin, 128
      of pyridines, 195
    and acids, of diazonium compounds, 437
      of diketone system, 32
      of dioxime, 59
      elimination of halogen atom by, 274, 367, 413
      of isatin, 126, 128
      of isatogenates, 125
      of isoxazoles, 404
      of ketones, 249, 255, 343
      of nitro group, 434
      of nitroso compound, 364, 444
      of N-nitroso compound, 111
      of olefin system, 458
      of oxime, 458
      of pyrroles, 71
      of quinone, 31
      of triazines, 513
    alcohol, and platinic chloride, elimination of halogen atom by, 253
    and alkali, of coumarins, 162
      of diketone system, 32
      of disulfides, 383
      of indoxyl, 123
      of nitro group, 122, 210

- Reduction, by zinc, and alkali, of rotenone, 172
    - of xanthone, 177
- Reduction potentials, of quinone compounds, 398
- Replacement, of carboxyl group, of iodo, 7
    - by mercuric chloride, 6
    - by nitro, 7, 44
  - of iodo atom by nitro group, 7
  - of nuclear oxygen in furan, 9
- Resonance, in acridine dyes, 339
  - in acridone, 334
  - in aminoacridines, 332
  - in barbituric acid, 488
  - in cyanine dyes, 294
  - in diketopiperazines, 504
  - in monocyclic compounds, 202
  - in naphthalene, 394
  - in phenazine dyes, 507
  - in quinoline system, 278
  - in semiquinone, 511
  - in triazines, 513
- Retencoxazole, 2-phenyl-, 419
- Rhodamines, 182
- Rhodanic acid, 415
- Rhodanine, 339, 429
  - N-allyl, 431
  - condensation of, with isatin, 471_{16}
  - N-phenyl, 431
  - products from, 430
- Rhodanine red, 430
- Rhodochlorin, 95
- Rhodoporphyrin, 88, 89
- Rhodoporphyrin XV, 90
- Riboflavin, 511
- Ribonucleic acid, 496
- Ribitylisoalloxazine, 512
- Ricinine, 220
- Ring enlargement, of indoles, 104
  - of isatin, 130, 273, 353, 383
  - of oximes of cyclic ketones, 231, 254, 274, 372, 499
  - of pyrroles, 61
- Ring instability in dihydro azoles, 373
- Ring opening, of azoles, 406
  - with cyanogen bromide, 240
  - of cyclic amides, 120
  - of cyclic ketones, 291
  - of dibenzofurans, 34
  - of furan compounds, 7
  - of imidazoles, 408, 455
- Ring opening, of pyrans, 149
  - of pyridine compounds, 199, 200
  - of pyrrols, 67
  - of thiazoles, 407
  - of thiophene compounds, 46
  - of tocopherols, 160
- Rivanol, 338
- Rosindoles, 118
- Rotenone, 172
- Rottlerin, 159
- Rottlerone, 159
- Ruban, 286
- 9-Rubanol, 6′-methoxy, 300_{15g}
  - 6′-methoxy-3-ethyl, 300_{21}
  - 6′-methoxy-3-vinyl, 287
- Rubatoxin, 286
- Rubazonic acid, 447
  - methyl-, 447
- Rubiazole, 364
- Rufigallic acid, 314
- Rutaecarpine, 501
- Rutonal, 491

- Saccharin, 438
- Sandoptal, 491
- Sanguinarine, 342
- Sarcosine anhydride, 504, 506
- Schiff base, polymerization of, 513
- Scopolamine, 247
- Selectan, 224
- Selenadiazole, 362
  - 3,5-diphenyl-1,2,4-, 468_{8e}
- Selenazole, 366
  - 2,5-diphenyl, 468_{8h}
  - 4-methyl-2-phenyl, 388
- Selenium dehydrogenation, 350
- Selenium dioxide, oxidation with, 277, 284
- Selenophene, 54_7
- Selenophthene, 54_7
- Selenotropinone, 239
- Selenoxanthone, 184_8
- Selenoxen, 54_7
- Semidine rearrangement, indole by, 101
  - phenazine by, 510
- Semiquinone, 511
- Sensitizers, cyanines (*see* Dyes, cyanine)
  - oxacyanines, 420
  - rhodanine, 431

Silver, color test for, 430
  complexes of (*see* Metal complexes)
Sinflavine, 338
Skatole, 103
Sodium alkoxides, alkylating agents in pyrroles, 63
Sodium amide, addition of, to phenanthridine, 342
    to pyridine, 194
    to quinoline, 276
Sparteine, 358
Spirochromans, 158
Spirohydantoin, 461
Substituents, effect on stability, of benzofuran compounds, 25, 34
    of furan compounds, 9
    of pyrrole compounds, 64
Succinimides, conversion of, to pyrroles, 57, 59
  formation of, from pyrroles, 68
Sucrose, conversion of, to furfural compounds, 3
Sugars, conversion of, to imidazoles, 450
Sulfa compounds, 486
Sulfa drugs, theory of action of, 427
Sulfadiazine, 486
Sulfapyridine, 222
Sulfasuxidine, 428
Sulfathiazole, 427
Sulfhydryl group, detection of, 463
Sulfonation, mild reagents for, 505
  of pyrroles, with chlorosulfonic acid, 64
Sulfonyl chlorides, preparation of, from thiocyanates, 486
Superaromaticity, in furan compounds, 9
  in thiophene compounds, 42
Sweet clover, active principle in, 164
Synergist, 174
Synthesis, Beyer quinoline, 264
  Biogenic, 239, 271, 302, 312
  Döbner and Miller's, 263, 273
  Döbner pyruvic acid, 264, 345
  Fisher indole, 101, 141, 267
    Reddelien's mechanism for, 102
    Robinson's mechanism for, 101
  Friedländer, 270
  Gattermann, 22, 23, 29, 414
  Hantzsch pyridine, 187
  Hantzsch pyrrole, 59
  Heumann indigo, 51, 122
  Hoesch, 175, 183
  Hofmann hypobromite, 454
Synthesis, Japp-Klingleman, 102, 375
  Knoevenagel pyridine, 274
  Knorr pyrrole, 57, 70
  Knorr quinoline, 265
  Kolbe, 61, 104, 249
  v. Niementowski, 272
  Paal-Knorr, 57
  Perkin, 5, 161
  Pictet and Hubert, 353
  Pschorr phenanthrene, 317, 343
  Reimer-Tiemann, 61
  Riehm quinoline, 264
  Skraup, 262, 280, 355
    with 1-chloro-2-naphthylamine, 395
    naphthoid and benzoid structures and, 394, 396
    with phenylenediamines, 343
    preparation of alizarin blue by, 355
      phenanthrolines by, 344
      phenotripyridine by, 394
    in synthesis of dimethylergoline, 352
      of quinoline carboxylic acids, 285
  Sommelet's benzaldehyde, 516
  Riedel, 498
  Robinson, tropinone, 238, 249
  Rosemund aldehyde, 212
  Ullmann, 210
    (*See also* Reactions)

T

Taste, peppery, 244
  sweet, 438
Tautomerism, in α-aminopyridine, 212
  in carbostyril, 281
  in isatin, 130
  in 1-phenyl-3-methylpyrazolone, 415
  in pyridones, 211
Tectoridin, 171
Telepathine, 348
Telluro cyclopentane-3,5-dione, 157
Tephrosin, 173
Tests, Adamkiewicz, 350
  Ehrlich, 68
  for formaldehyde, 318
  for Grignard reagent, 197
  Hopkins-Cole, 115, 118
  indophenine (*see* Indophenine)
  Liebermann's, 47
  for metal ions (*see* Metal complexes)
  opium, 318

Tests, pine splinter (*see* Pine-splinter test)
    (*See also* Furan, Thiophene, Pyrroles, and other classes of compounds)
Tetrahydroharmin, 349
Tetrahydronaphthalene, benzoic structure of, 395
Tetrahydropyranyl-4-acetic acid, 237
Tetrahydrothiophene, 45
Tetrahydrotubaic acid, 27
Tetralin, benzoic structure of, 395
Tetrapyrryl compounds, 79
Tetrapyrrylethane, 76
Tetrazines, 517
Tetrazole, 5-phenyl, 365
  1-phenyl-5-mercapto, 380
  2-phenyl-5-methyl, 466
Tetrazoles, 464
  acidity of, 405
  boiling points of, 390
  hydrolysis of, 407
  preparation of, 374, 376
Tetrazolium salt, 376
Thalloperazine, 510
Thebaine, 318
Theobromine, 493–495
  synthesis of, 519_{11}
Theophylline, 493, 494
  synthesis of, 519_{11}
Therapeutic activity, of acridine compounds, 339
    (*See also* Physiological activity)
Thiadiazoles, 365, 464
  boiling points of, 390
  preparation of, 374
Thiamin, 486
Thiamine chloride, 428
  thiazole half of, 428
Thiazine, 476
Thiazole, 2-amino, 427
  2-benzyl, 388
  2-chloro, 366
  2,4-dimethyl-5-phenyl, 388
  2,5-dimethyl-5-phenyl, 388
  4-methyl-5-(β-hydroxyethyl), 428
  methylphenyl, 388, 471_{12}
  methyltolyl, 388
  phenyl, 388
Thiazole-5-carboxylic acid, 4-methyl, 428
Thiazoles, 427
  boiling points of, 389, 390
  bromination of, 400
  nitration of, 400
Thiazoles, reaction of, with hydroxylamine, 404
  solubility of, in water, 386
  sulfonation of, 400
  synthesis of, 364
    comparison of, with azines, 476
Thiazolidines, 2,4-dioxo-5,5′-dialkyl, 432
Thiazolidone-4, 2-mercapto, 429
Thiazolines, 419
  2-methyl, 436
Thiazolones, comparison of, with barbiturates, 432
Thiazolyl chlorides, 429
Thieno[3,2-*b*]thiophene, 49
Thienylsodium, 6
Thioacridine, 333
Thioanthranil, 388
Thiochrome, 487
Thiocyanation, 385
Thiocyano group, introduction of, in pyrroles, 65
Thiohydantoin, 415
Thioindigo dyes, 51
    (*See also* Dyes)
Thioindoxyl, 52
Thioisatinanilide, 430
Thional, 481
Thionaphthene, 49
  nitro, 50
Thionaphthene compounds, 49
Thionaphthene-3-acetic acid, 51
Thionaphthene-3-carboxylic acid, 50
Thionaphthenopyrazole, 449
Thionessal, 49
α-Thiophenaldehyde, 47
Thiophene, 39
  4-benzamido-3-ketotetrahydro, 457
  2,3-dichloro, 48
  2,5-dimethyl, 47
  2,3,4,5-di(1,8-naphthylene)-, 45
  2-ethyl-5-methyl, 48
  α-methyl, 40
  2-nitro, 41, 48
α-Thiophene carboxylic acid, 40
  2,3-dibromo, 48
Thiophene compounds, 41, 54_{2}
  chemical properties of, 42
  comparison of, with benzene series, 41, 389
  condensed, 49
  dehydrogenation of, 45
  directing influence in, 43

- Thiophene compounds, physical properties of, 41
  - preparation of, 40
  - tests for, 46
- Thiophenin, 48
- Thiophenols, preparation of, from benzene sulfonyl chloride, 52
  - from disulfides, 383
- Thiophthene, 49
- Thiopyrine, 444
- Thiosemicarbazide, in preparation of azoles, 375
- Thiotolene, 42
- Thiotropinone, 239
- Thioxanthone, 179
- 2,5-Thioxen, 47
- Thymine, 493, 496
- Tocopherols, 159
- Toxicarol, 173
- Triazines, 513
  - trinitrohexahydro, 516
- 1,2,3-Triazole, 1-phenyl-5-amino-, 465
  - 1-phenyl-4-carbethoxy-5-hydroxy, 466
- 1,2,4-Triazole, 374
  - 4-amino, 368
- 1,3,4-Triazole, 1,2,5-triphenyl, 466
- Triazoles, 464
  - acidity of, 405
  - basicity of, 405
  - boiling points of, 390
  - decomposition of, to form carbazoles, 141
  - N-phenyl, 471$_{12}$
  - in preparation of carbolines, 347
  - ring opening of, 408
  - substitution in, 402
- Triazolones, 416
- Trigenin, 444
- Trigonelline, 228$_{19}$
- Trimethylenetrisulfoxide, 517
- Triphenylisoxazole, and Beckmann rearrangement, 422
  - preparation of, 377
- Triphenylmethyl, addition of, to pyrroles, 65
- Triphosphopyridine nucleotide, 497
- Tripyrrole, 66
- Tripyrryl compounds, 79
- Tripyrrylmethanes, 77
- Trithiane, 517
- Trithiole, 364
- Troger's base, 500
- Tropic acid, 247
- Tropine, 248
- Tropinone, 238
- Truxilline, 249
- Trypaflavine, 338, 339
- Tryptamine, 115
- Tryptophan, 114
  - Adamkiewicz test for, 350
- Tryptophan nucleus, in harman, 349
  - in isoquinoline alkaloids, 312
  - in lysergic acid, 351
- Tubaic acid, 28, 173
  - reduction of, 24
- Tubatoxin, 172
- Tutocaine, 250
- Tyramine, 453

U

- Umbelliferone, 162
- Uracil, 492, 496
- Uramil, 495
- *p*-Urazine, 518
- Urazole, 465
  - phenyl, 466
  - tolyl, 466
- Urease, 463
- Uric acid, 494, 495
  - conversion of, to allantoin, 461
- Uroporphyrin, 85, 91
- Uroselectan, 224
- Uroselectan B, 224
- Urotropine, 516
- Usneol, 39
- Usnic acid, 29

V

- Vasicine, 501
- Vasodilator, histamine as, 453
- Veronal, 491
- N-Vinylcarbazole, 142
- Vinylogous system, in γ-pyrone, 150
- Vinylogy, in pyrroles, 62
- Vinylpyridine, 228$_{20}$
- Violanin, 166
- Violuric acid, 495
- Vitamin B complex, 486
- Vitamins
  - B$_1$, 428, 486
  - B$_2$, 214
  - B$_6$, 221

- Vitamins, C, 17
  - E, 21, 30, 159
  - H, 458
  - P, 170
- Vitimidazole, 471_{13}
- Voluntal, 444
- Vulcanization accelerator, 437

W

- Warburg's ferment, 497
- Water, and solubility, of azoles, 386
    - of heterocyclic compounds, 386
    - of nicotine, 217
    - of pyrazines, 503
    - of pyridinium hydroxides, 199
    - of pyrimidines, 485
- Wiechowskii's reagent, 460
- Woad, 133

X

- Xanthenes, 176
- Xanthine, 494
- Xanthoapocyanine, 295
- Xanthone, 148, 177
- Xanthotoxin, 163
- Xanthydrols, 180
- Xanthylium salts, 180

Y

- Yageine, 348
- Yatren, 282
- Yobyrin, 350
- Yohimbine, 348, 349

Z

- Zerewitinov test, of bilirubin, 79
  - of indigo-copper complex, 136
  - of oxindole, 120
  - of porphyrins, 83
  - of pyrrole compounds, 63
  - of rotenone, 173
- Zinc-dust distillation, of acridone, 329, 333
  - anthrazine by, 511
  - of carboline compound, 347
  - of coniine, 245
  - to eliminate hydroxy groups, 36
  - first example of, 100
  - of lobeline, 252
  - of morphine, 318
  - of oxindole, 100
  - of phenanthridone, 342
  - of rosinduline, 510
  - of xanthones, 177